

# A Practical Guide to Human Cancer Genetics

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Fourth Edition



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## Foreword for the 4th Edition

Though cancer is essentially a genetic disease at the cellular level and mostly not clearly inherited, studies of familial cancers are not only interesting in their own right but have also made a major contribution to the identification of key genetic changes at the somatic level during cancer progression. The genetics of cancer at the germline level remains one of the most exciting and interesting developments in cancer research, if anything increasingly so with the enormous developments in the technology of DNA sequencing. This has made it possible to recognize the genetic basis of quite rare inherited conditions, sometimes based on only a few cases in only a single family. The new technologies have also made much more widespread testing of families for the presence of the commoner clearly inherited cancer susceptibilities economically feasible. Cancer genetics in this sense has thus become a major part of the workload of clinical genetics services.

Human genetics at the clinical level traditionally focused largely on congenital and pediatric problems. Cancer families, however, pose a completely different problem, since they mostly involve genetic susceptibilities with a late age of onset, offering in most cases the opportunity for effective intervention once individuals at risk have been identified. Such families can provide intriguing opportunities for testing the effectiveness of the removal of early cancers or precancerous growths.

The range of hereditary cancers is quite extraordinary, even though many are individually quite rare. They provide a unique source of material for understanding the carcinogenic process and a major challenge to the human and clinical geneticist.

This fourth edition of the book, originally published in 1992 by Shirley Hodgson and Eamonn Maher, is a substantial reworking of the first edition that takes into account the major developments over the last 20 years, with the addition of two new authors, William Foulkes and Charis Eng to the third and fourth editions. In addition to providing information on many new genes involving strong inherited susceptibility, there is increased coverage of lower-penetrance genes, possibilities for new therapies, and updated screening information. The new edition will be most

valuable as an up-to-date account of cancer genetics with a comprehensive survey of a wide range of cancer predispositions, gathered together in a form that will be of great practical value to the clinician but also of great interest for the basic laboratory scientist.

May 27, 2013

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# Preface

Since the third edition of this book, the rapid development in our understanding of inherited cancer susceptibility has continued apace. This edition is the first to be published by Springer, and the change in publisher has been accompanied by a thorough revision and updating on the whole book to reflect the numerous cancer gene discoveries since the last edition and the increasing relevance of genetic information for prognosis and management of individuals with or at risk of inherited cancers.

Although novel discoveries facilitated by technological advances (e.g., high-throughput second-generation sequencing) are often the most high-profile developments in cancer genetics, it remains true that improving the care of families affected by inherited cancers mainly uses information about highly penetrant genes and requires a well-coordinated multidisciplinary approach. Engaging families by sensitive counseling practices for predictive testing and awareness of psychosocial, insurance, and ethical issues remain fundamental to the delivery of an excellent clinical service. This edition of this book takes into account the many new developments in our understanding of cancer genetics – ranging from molecular pathways of oncogenesis to the translation of scientific knowledge into the development of novel clinical and diagnostic services. This edition reflects current clinical practice in Europe and North America and should therefore be of wide utility to those interested in clinical cancer genetics internationally.

Cancer genetics now accounts for at least half of the workload in most comprehensive genetics centers, and a knowledge of this discipline is now germane to an enormous range of specialties. Additionally, the increasing mainstreaming of cancer genetics means that clinicians from many disciplines will need to gain insight into details of cancer genetics. We therefore hope and believe that the popularity of previous editions of this book will sustain and enhance this edition and will be helpful to the many clinicians, laboratory scientists, and healthcare professionals who are faced with the ever-enlarging demand for knowledge of familial cancer risks.

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# Contents

<b>1</b>	<b>Central Nervous System</b>	<b>1</b>
	Vestibular Schwannoma (Acoustic Neuroma)	2
	Choroid Plexus Tumor	2
	Ependymoma	3
	Gliomas (Including Astrocytoma and Glioblastoma)	3
	Hemangioblastoma	4
	Hemangioma	5
	Medulloblastoma	5
	Meningioma	6
	Nerve Root Tumors	6
	Neuroblastoma	7
	Pineal Tumor	8
	Primitive Neuroectodermal Tumors	8
	References	9
<b>2</b>	<b>Eye</b>	<b>15</b>
	Retinoblastoma	15
	Retinal Astrocytic Hamartoma	19
	Optic Glioma	19
	Ocular Choristoma	20
	Ciliary Body Medulloepithelioma	20
	Cavernous Hemangioma	20
	Hemangioblastoma	20
	Melanoma	21
	Meningioma	22
	References	22
<b>3</b>	<b>Cardiorespiratory System and Thorax</b>	<b>25</b>
	Head and Neck Cancer	25
	General	25
	Specific Sites	26
	Tumors of the Lung	27

Mesothelioma . . . . .	28
Cardiac Tumors . . . . .	28
References . . . . .	29
<b>4 Endocrine System . . . . .</b>	<b>31</b>
Thyroid Tumors . . . . .	31
Papillary Thyroid Carcinoma (PTC) . . . . .	31
Follicular Thyroid Carcinoma (FTC) . . . . .	33
Medullary Thyroid Carcinoma (MTC) . . . . .	33
Benign Neoplasia of the Thyroid . . . . .	34
Parathyroid Tumors . . . . .	34
Pituitary Tumors . . . . .	35
Adrenal Gland Tumors . . . . .	36
Pheochromocytoma . . . . .	36
Adrenocortical Adenoma and Carcinoma . . . . .	39
Glomus Tumors (Non-chromaffin Paraganglioma) . . . . .	40
Pancreatic Endocrine Tumors . . . . .	41
References . . . . .	41
<b>5 Gastrointestinal System . . . . .</b>	<b>47</b>
Salivary Gland Tumors . . . . .	47
Gastrointestinal System . . . . .	48
Esophageal Tumors . . . . .	48
Management . . . . .	50
Gastric Tumors . . . . .	50
Gastric Carcinoma . . . . .	51
Hepatic Tumors . . . . .	53
Hepatoblastoma . . . . .	53
Hepatocellular Carcinoma . . . . .	53
Cholangiocarcinoma of the Liver . . . . .	56
Hepatic Angiosarcoma . . . . .	56
Tumors of the Gallbladder . . . . .	57
Pancreatic Cancer . . . . .	57
Tumors of the Small Intestine . . . . .	60
Gastrointestinal Polyposis . . . . .	62
Tumors of the Colon and Rectum . . . . .	63
Identification of High-Risk Families . . . . .	67
Pathological Features . . . . .	69
Surveillance Strategies . . . . .	69
Chemoprophylaxis . . . . .	71
References . . . . .	72
<b>6 Reproductive System . . . . .</b>	<b>89</b>
Breast Cancer . . . . .	89
Background: Epidemiology and Family History . . . . .	89
BRCA1 and BRCA2 . . . . .	91
The Genes and the Risks for Cancer . . . . .	91

BRCA Protein Function . . . . .	93
Other Genes Involved in Breast Cancer Susceptibility . . . . .	95
Histopathology of Breast Cancer and Its Relationship to Genetics. . . .	97
Genetic Counseling . . . . .	98
Screening and Prophylaxis. . . . .	99
Uterine Tumors . . . . .	101
Uterine Leiomyoma . . . . .	101
Carcinoma of the Uterus . . . . .	102
Choriocarcinoma . . . . .	104
Fallopian Tube Carcinoma. . . . .	104
Ovarian Cancer . . . . .	105
Ovarian Carcinoma . . . . .	105
Other Ovarian Neoplasms . . . . .	112
Cancer of the Cervix . . . . .	113
Other Tumors of the Female Reproductive System. . . . .	114
Cancer of the External Genitalia . . . . .	114
Vaginal Carcinoma. . . . .	114
Prostate Cancer . . . . .	115
Testicular Neoplasms. . . . .	117
Testicular Tumors in Intersex States . . . . .	119
Epididymal Tumors . . . . .	121
References . . . . .	121
<b>7 Urinary System. . . . .</b>	<b>137</b>
Renal Neoplasms . . . . .	137
Wilms Tumor. . . . .	137
WAGR Syndrome (Wilms Tumour-Aniridia-Genital Abnormality-Mental Retardation) and the WT1 Gene . . . . .	138
Renal Cell Carcinoma (Adenocarcinoma, Hypernephroma) . . . . .	140
Cancer of the Ureter and Renal Pelvis. . . . .	141
Bladder Cancer. . . . .	142
References . . . . .	143
<b>8 Blood and Lymph. . . . .</b>	<b>145</b>
Leukemia . . . . .	145
Acute Lymphoblastic Leukemia (ALL) . . . . .	146
Acute Myeloid (Myelogenous) Leukemia . . . . .	147
Chronic Myeloid Leukemia . . . . .	148
Chronic Lymphocytic Leukemia. . . . .	149
Polycythemia. . . . .	152
Thrombocythemia. . . . .	153
Lymphoma . . . . .	153
Hodgkin Disease . . . . .	154
Non-Hodgkin Lymphoma . . . . .	156
Myeloma . . . . .	157
Waldenstrom Macroglobulinemia . . . . .	158
Histiocytoses . . . . .	158
References . . . . .	159

<b>9 Musculoskeletal System</b> . . . . .	167
Bone Tumors . . . . .	167
Osteosarcoma . . . . .	167
References . . . . .	173
<b>10 Skin</b> . . . . .	177
Specific Skin Cancers . . . . .	177
Genetic Predisposition to Melanoma . . . . .	178
Familial Melanoma . . . . .	180
Giant Congenital Melanocytic Nevus . . . . .	185
Basal Cell Carcinoma (BCC) . . . . .	185
Bazex Syndrome (Bazex–Dupré–Christol Syndrome) . . . . .	187
Rombo Syndrome . . . . .	189
Squamous Cell Carcinoma (SCC). . . . .	189
Epidermodysplasia Verruciformis . . . . .	190
Ferguson-Smith-Type Self-Healing Epithelioma (Multiple Self-Healing Squamous Epithelioma). . . . .	190
Inherited Conditions Predisposing to Dermatological Malignancy . . . .	192
Albinism . . . . .	192
Birt–Hogg–Dubé Syndrome . . . . .	192
Brooke–Spiegler Syndrome (Multiple Cylindromatosis) . . . . .	192
Cheilitis Glandularis . . . . .	193
Chronic Mucocutaneous Candidiasis Syndrome . . . . .	193
Congenital Generalized Fibromatosis . . . . .	194
Dyskeratosis Congenita. . . . .	194
Ectodermal Dysplasias . . . . .	195
Epidermolysis Bullosa . . . . .	195
KID Syndrome . . . . .	196
Multiple Cylindromatosis . . . . .	197
Flegel Disease (Hyperkeratosis Lenticularis Perstans). . . . .	197
Juvenile Hyaline Fibromatosis . . . . .	197
Klippel–Trenaunay Syndrome . . . . .	198
Lichen Planus . . . . .	198
Porokeratosis of Mibelli . . . . .	198
Proteus Syndrome . . . . .	199
Sclerolytosis (Scleroatrophic and Keratotic Dermatitis of Limbs; Scleroatrophic Syndrome of Huriez) . . . . .	199
Steatocystoma Multiplex. . . . .	200
Syringomas . . . . .	200
Trichoepithelioma . . . . .	200
Tylosis . . . . .	200
Lichen Sclerosis Et Atrophicus . . . . .	201
Mast Cell Disease . . . . .	201
Multiple Cutaneous Leiomyomas . . . . .	201
Multiple Lipomatosis: Familial. . . . .	202
Multiple Lipomatosis: Symmetric. . . . .	202

NAME Syndrome: Carney Complex . . . . .	203
Pachyonychia Congenita . . . . .	203
Palmar Keratoses . . . . .	204
Pilomatrixoma (Benign Calcifying Epithelioma of Malherbe) . . . . .	204
References . . . . .	205
<b>11 Inherited Cancer-Predisposing Syndromes . . . . .</b>	<b>219</b>
Ataxia Telangiectasia (OMIM 208900) . . . . .	219
Ataxia-Telangiectasia-Like Disorder (ATLD) (OMIM 604391) . . . . .	220
Bannayan–Riley–Ruvalcaba Syndrome (Bannayan–Zonana Syndrome, Ruvalcaba–Riley–Smith Syndrome) . . . . .	221
Beckwith–Wiedemann Syndrome (EMG Syndrome and IGF2 Overgrowth Disorder) (OMIM 130650) . . . . .	221
Birt–Hogg–Dubé Syndrome (OMIM 135150) . . . . .	224
Blackfan–Diamond Syndrome (OMIM 105650) . . . . .	225
Bloom Syndrome (OMIM 210900) . . . . .	226
Blue Rubber Bleb Nevus Syndrome (OMIM 112200) . . . . .	227
Carney–Stratakis Syndrome (Carney Dyad; Dyad of Paragangliomas and Stromal Tumors) (OMIM 606864) . . . . .	228
Carney Complex (NAME Syndrome, LAMB Syndrome, Carney Syndrome) (OMIM 160980) . . . . .	228
Cockayne Syndrome (OMIM 216400) . . . . .	230
Celiac Disease . . . . .	231
Common Variable Immunodeficiency (CVID) (OMIM 607594) . . . . .	232
Constitutional Mismatch Repair Deficiency (CMMRD), also known as Autosomal Recessive Childhood Cancer Predisposition Syndrome (OMIM 276300) . . . . .	232
Costello Syndrome (OMIM 218040) . . . . .	232
Cowden Syndrome (Multiple Hamartoma Syndrome) (OMIM 158350) . . . . .	233
Denys–Drash Syndrome (OMIM 194080) . . . . .	239
Down Syndrome (OMIM 190685) . . . . .	240
Familial Adenomatous Polyposis (OMIM 175100) . . . . .	241
Management . . . . .	246
Fanconi Anemia (OMIM 227650) . . . . .	249
Frasier Syndrome (OMIM 136680) . . . . .	252
Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome) (OMIM 109400) . . . . .	252
Hemihypertrophy/Hemihyperplasia . . . . .	255
Hereditary Non-polyposis Colorectal Cancer, Lynch Syndrome (OMIM 120435) . . . . .	256
Background: History and Epidemiology . . . . .	256
Clinical Features and Pathology . . . . .	257
Diagnostic Features . . . . .	258
Molecular Genetics . . . . .	261
Extracolonic Cancer in Lynch Syndrome . . . . .	262



Screening. . . . .	263
Genetic Counseling in Lynch Syndrome. . . . .	265
Hyperparathyroidism–Jaw Tumor Syndrome (CDC73-Related Disorders) (OMIM 145001). . . . .	266
Juvenile Polyposis Syndrome (JPS) (OMIM 174900). . . . .	267
Clinical Surveillance . . . . .	269
Klinefelter Syndrome. . . . .	270
Kostmann Syndrome (Kostmann Infantile Agranulocytosis, SCN3,) (OMIM #610738) . . . . .	270
Li–Fraumeni Syndrome (OMIM #151623) . . . . .	271
Clinical Features . . . . .	271
Genetics. . . . .	272
Genetic and Medical Management . . . . .	274
Maffucci Syndrome (OMIM 166000) . . . . .	274
McCune–Albright Syndrome (OMIM 174800). . . . .	275
Mosaic Variegated Aneuploidy Syndrome 1 (OMIM #257300) . . . . .	277
Mosaic Variegated Aneuploidy Syndrome 2 (OMIM #614114) . . . . .	277
Multiple Endocrine Neoplasia Type 1 (OMIM 131100) and the <i>CDKN</i> -opathies . . . . .	278
Clinical Features . . . . .	278
Genetics. . . . .	279
Genetic and Medical Management . . . . .	280
Multiple Endocrine Neoplasia Type 2 MEN 2 – OMIM 171400 . . . . .	281
Multiple Endocrine Neoplasia Type 2A . . . . .	282
Multiple Endocrine Neoplasia Type 2B . . . . .	282
Familial Medullary Thyroid Carcinoma . . . . .	283
Molecular Genetics of MEN 2 . . . . .	283
Molecular-Based Medical Management in MEN 2 . . . . .	285
Muir–Torre Syndrome (OMIM 158320) . . . . .	286
MUTYH-Associated Polyposis (MAP) (OMIM 608456) . . . . .	287
N Syndrome (OMIM 310465) . . . . .	288
NAME Syndrome . . . . .	288
Neurofibromatosis Type 1 (NF1) (Von Recklinghausen Disease, Peripheral NF) (OMIM 162200) . . . . .	288
Specific Tumor Types in NF1 . . . . .	290
Neurofibromatosis Type 2 (NF2) (Central Neurofibromatosis and Bilateral Acoustic Neuroma Neurofibromatosis) (OMIM 607379) . . . . .	293
Neurofibromatosis: Atypical . . . . .	296
Nijmegen Breakage Syndrome, NBS (also known as Seemanova Syndrome II) (OMIM #251260). . . . .	296
Noonan Syndrome (OMIM 163950) and the RASopathies. . . . .	297
Perlman Syndrome (OMIM 267000). . . . .	298
Peutz–Jeghers Syndrome (PJS) (OMIM 602216, OMIM 175200) . . . . .	299
Clinical Features . . . . .	299

Genetics . . . . .	300
Genetic and Medical Management . . . . .	301
Pleuropulmonary Blastoma – Familial Tumor Dysplasia Syndrome (PPB-FTDS) (OMIM #601200, #138800) . . . . .	301
Porphyria . . . . .	302
Rhabdoid Tumor Predisposition Syndrome 1 (OMIM #609322) . . . . .	303
Rhabdoid Tumor Predisposition Syndrome 2 (OMIM #613325) . . . . .	303
Rothmund–Thomson Syndrome (OMIM 268400) . . . . .	304
Severe Combined Immunodeficiency Disease (OMIM 102700) . . . . .	305
Shwachman–Diamond Syndrome (OMIM 260400) . . . . .	305
Simpson–Golabi–Behmel Syndrome (OMIM 312870) . . . . .	306
Sotos Syndrome (OMIM 117550) . . . . .	307
Tuberous Sclerosis (Tuberosc Sclerosis) (OMIM 191100 and 191092) . . . . .	307
Turcot Syndrome (OMIM 276300 and 175100) . . . . .	311
Turner Syndrome . . . . .	312
Tylosis (Keratosi Palmaris et Plantaris) (OMIM 148500) . . . . .	312
Von Hippel–Lindau Syndrome (OMIM 193300) . . . . .	313
Cerebellar Hemangioblastoma . . . . .	314
Spinal Cord Hemangioblastoma . . . . .	314
Brain Stem Hemangioblastoma . . . . .	314
Retinal Angiomas . . . . .	315
Renal Cell Carcinoma . . . . .	316
Pheochromocytoma . . . . .	316
Pancreas . . . . .	317
Endolymphatic Sac Tumors (ELSTs) . . . . .	317
Molecular Genetics . . . . .	317
Werner Syndrome (OMIM #277700) . . . . .	318
Wiskott–Aldrich syndrome, OMIM #301000; X-Linked Thrombocytopenia, #313900; Intermittent X-Linked Thrombocytopenia, #313900; and X-Linked Neutropenia, #300299 . . . .	319
X-Linked Lymphoproliferative Disorder (Duncan Disease) (OMIM 308240) . . . . .	320
Xeroderma Pigmentosum (OMIM #278700, 610651, 278720, 278730, 278740, 278760, 278780, and variant 278750) . . . . .	320
References . . . . .	322
<b>Appendix</b> . . . . .	361
Genetic Differential Diagnoses by Organ System Neoplasms . . . . .	361
References . . . . .	377
<b>Index</b> . . . . .	405



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# Chapter 1

## Central Nervous System

Primary central nervous system (CNS) neoplasms affect about 1 per 10,000 of the population. Although the incidence of brain tumors increases with advancing age, intracranial neoplasms are the most common cause of solid cancer in children. The distribution and histological type of brain tumor differ in children and in adults. In children, brain tumors most often arise in the posterior fossa, and the most frequent tumor types are medulloblastoma, spongioblastoma (including cerebellar astrocytoma and optic nerve glioma), and ependymomas. In adults, most tumors are supratentorial, and meningiomas and gliomas are the most frequent types. Familial brain tumors may occur as part of a rare specific inherited cancer syndrome (Table 1.1). Epidemiological studies have suggested that there is a small increased risk of cerebral neoplasms among relatives of brain tumor patients compared to controls: Choi et al. (1970) and Gold et al. (1994) found a ninefold increase in the incidence of brain tumor among relatives of patients with glioma compared to controls, whereas Burch et al. (1987) found a (statistically insignificant) sixfold increase among relatives of brain tumor patients. Nevertheless, the absolute risk to relatives is small, 0.6 % in the study by Choi et al. (1970). Miller (1971) found a ninefold increase in the expected number of sib pairs among children with brain tumors and a similar excess of families in which one child died of brain tumor and another of cancer of bone or muscle. Soft tissue sarcomas and brain tumors occur as part of the Li–Fraumeni syndrome. Mahaley et al. (1989) found a family history of cancer in 16–19 % of patients with brain tumors (similar to the expected incidence) but that the incidence was 30–33 % in patients with glioblastoma multiforme, malignant lymphoma, and neuroblastoma. A family history of neurofibromatosis was obtained in 1.6 % of cases. In a recent large joint Nordic study, 2.6 % of patients with nervous system cancer were familial. The SIR of brain tumors was 1.7 in offspring of affected parents, 2.0 in siblings, and 9.4 in families with a parent and sibling affected (Hemminki et al. 2010). As high-penetrance multiplex families with CNS tumors accounted for only a minority of cases, it has been suggested that most familial risks might be attributable to lower-penetrance genes (Hemminki et al. 2009). The familial risks for nervous system tumors do vary according to tumor histopathology (Hemminki et al. 2009), and the genetic implications of specific CNS tumors are described below.

**Table 1.1** Genetic disorders associated with tumors of the CNS

Neurofibromatosis type 1
Neurofibromatosis type 2
von Hippel–Lindau disease
Li–Fraumeni syndrome
Familial adenomatous polyposis
Turcot syndrome (including homozygous mismatch gene mutations)
Tuberose sclerosis
Gorlin syndrome
Ataxia telangiectasia
Werner syndrome
Blue rubber bleb nevus syndrome

Details of individual conditions are given in Chap. 11

**Vestibular Schwannoma (Acoustic Neuroma)**

This tumor accounts for around 8 % of all intracranial tumors and has an incidence of 13/million per year (Tos and Thomsen 1984). Although sometimes called acoustic neuromas, these are Schwann cell tumors. They usually arise from the vestibular nerve but can develop on the fifth cranial nerve and less often on the ninth and tenth nerves. Within the spinal canal, they usually arise on the dorsal spinal root. Familial and bilateral vestibular schwannomas are features of neurofibromatosis type 2 (NF2). About 4 % of vestibular schwannomas are bilateral, and all patients with bilateral tumors have NF2 (see p. 293). Sporadic vestibular schwannoma is typically seen in the fifth and sixth decades of life, which is about 20 years later than in patients with NF2. The clinical features and diagnostic criteria for NF2 are discussed on p. 293. Although vestibular schwannoma in NF2 is usually bilateral, it can be unilateral. Those mosaics for an *NF2* gene mutation may present with milder- and later-onset disease (see p. 294).

Multiple extracranial schwannomas (cutaneous and spinal) without vestibular schwannomas may be inherited as a dominant trait (Evans et al. 1997) and may be caused by germline mutations in *SMARCB1* (see *Nerve Root Tumors below*). Occasionally *SMARCB1* mutations have been described in individuals with unilateral vestibular schwannomas and multiple central and cutaneous schwannomas (Smith et al. 2011).

**Choroid Plexus Tumor**

Choroid plexus neoplasms are rare (0.5 % of all brain tumors) and are most frequent in infancy. The majority of choroid plexus tumors are benign papillomas, but up to 30 % are classified as carcinomas.

Childhood choroid plexus tumors in sibling pairs have been reported and autosomal recessive inheritance suggested (Zwetsloot et al. 1991). Tumors of the choroid

plexus have been reported in the X-linked disorder Aicardi syndrome (Robinow et al. 1986). Germline *TP53* mutations are relatively frequent in children with choroid plexus tumors (Gozali et al. 2012). Though the family history may be suggestive of Li–Fraumeni syndrome in many cases, in others there may be no family history of cancer (Krutikova et al. 2005; Tabori et al. 2010). The germline founder *TP53* mutation R337H occurs at high frequency in Brazil and can be detected in most children who develop choroid plexus carcinomas (Custodio et al. 2011).

Choroid plexus angiomas were reported in two out of four patients with Perlman syndrome (p. 298) reported by Henneveld et al. (1999).

Choroid plexus tumors should be differentiated from endolymphatic sac tumors, which are a feature of von Hippel–Lindau disease (p. 313).

## Ependymoma

These glial cell tumors of the brain and spinal cord occur both sporadically and in association with cancer susceptibility syndromes. In children, the tumor usually presents as a posterior fossa mass. Ependymoma may be a feature of neurofibromatosis type 2 (see p. 293) and has rarely been reported as part of Turcot syndrome (Torres et al. 1997), multiple endocrine neoplasia type 1, and in association with a germline *P53* mutation. Familial ependymoma consistent with autosomal dominant inheritance with incomplete penetrance has also been described (Gilchrist and Savard 1989; Nijssen et al. 1994).

## Gliomas (Including Astrocytoma and Glioblastoma)

Astrocytoma and glioblastoma account for about 4 % of brain tumors in childhood and 17 % in adults. Genetic conditions associated with a predisposition to glioma include neurofibromatosis type 1 (NF1) (p. 288), NF2, Li–Fraumeni syndrome (p. 271), tuberose sclerosis (p. 307), Gorlin syndrome (p. 252), Turcot syndrome (p. 311), and Maffucci syndrome (p. 274). The precise tumor type in some cases can be correlated with specific disorders, for example, in tuberose sclerosis a benign astrocytic tumor (subependymal nodule) is typically seen, although giant cell astrocytoma can occur. However, in NF1 and Turcot syndrome, both astrocytoma and glioblastoma multiforme may be seen. Kibirige et al. (1989) found that of 282 children with astrocytoma, 21 had neurofibromatosis and 4 had tuberose sclerosis, and there was evidence that a similar proportion might have had Li–Fraumeni syndrome.

Familial glioma not associated with the inherited syndromes described above occurs, but is uncommon. In a review by Vieregge et al. (1987), of 39 reports, most (60 %) were of affected siblings, and one-quarter was of affected twins or of individuals with affected relatives in two generations. There were three pairs of monozygotic twins with glioma. In most affected sibling cases, the onset in the

second sibling was usually within 5 years of that of the first sibling. A high incidence of cerebral glioma was found in an isolated inbred community by Armstrong and Hanson (1969) and Thuwe et al. (1979). Glioblastoma multiforme is rare in children, but Duhaime et al. (1989) reported an affected sib pair aged 2 and 5 years with simultaneous onset of symptoms.

Rare families have been reported with a combination of melanoma and gliomas. In some families submicroscopic germline deletions of 9p21 have been identified which completely or partially involve *CDKN2A*±*CDKN2B* (Bahuaui et al. 1998; Tachibana et al. 2000). The *CDKN2A* locus encodes two gene products, p14 and p16, and there is evidence that p14 loss is critical for this disorder (Randerson-Moor et al. 2001). Thus, in brain tumor–melanoma kindreds, deletion studies of this region may be warranted if clinical testing for *CDKN2A* mutations has been undertaken and is negative.

In general, candidate gene analysis in non-syndromic familial glioma cases has been largely unproductive. Thus, although a study from the Mayo Clinic of 15 brain cancer patients who had a family history of brain tumors found that one had a germline *TP53* mutation, and another had a germline hemizygous deletion of the *CDKN2A/CDKN2B* region (Tachibana et al. 2000), a more recent, larger analysis ( $n=101$ ) of familial glioma cases did not detect germline *CDKN2A* mutations and only one *TP53* mutation (Robertson et al. 2010).

In the light of the evidence that lower-penetrance genes might represent a major contribution to familial risks for nervous system tumors (Hemminki et al. 2009), large collaborations such as the GLIOGENE consortium have undertaken genome-wide association studies and identified a number of polymorphic variants that predispose to glioma (Scheurer et al. 2010; Shete et al. 2011). Among the genes linked with susceptibility variants are *TERT*, *EGFR*, *CDKN2A/CDKN2B*, and *PHLDB1*, but only a small part of familial risk can be explained by the linked variants (Shete et al. 2009, 2011).

## Hemangioblastoma

These vascular tumors occur most frequently in the cerebellum followed by the spinal cord, brain stem, and, least frequently, supratentorially. Approximately 30 % of all cerebellar hemangioblastomas occur as part of von Hippel–Lindau (VHL) disease (see p. 313). Patients with multiple CNS hemangioblastomas satisfy the clinical diagnostic criteria for VHL disease. Hemangioblastoma is a benign tumor but may recur if surgical removal is not complete. In such cases the possibility of a new primary (and hence a diagnosis of VHL disease) should also be considered. The risk of VHL disease is highest in younger patients: the mean ages at diagnosis of cerebellar hemangioblastoma in this disease and in nonfamilial cases are 29 and 48 years, respectively (Maher et al. 1990). All patients with apparently sporadic hemangioblastomas should be screened for subclinical evidence of VHL disease. In addition, *VHL* mutation analysis is helpful, particularly in patients aged less than 50 years. Germline *VHL* gene mutations were detected in 4 % of apparently sporadic hemangioblastoma cases without clinical or radiological evidence of VHL



disease (Hes et al. 2000). In view of the possibility of false-negative mutation analysis results (e.g., if mosaic), younger patients (less than 40 years) may be kept under review in case evidence of VHL disease develops later.

## Hemangioma

Cavernous hemangiomas may occur sporadically or as a familial trait when they are inherited as a dominant trait with incomplete penetrance (Riant et al. 2010). Familial cases, which account for about 20 % of the total, frequently develop multiple cavernous hemangiomas, but these may be asymptomatic and only detected by magnetic resonance imaging (MRI) scanning. Retinal cavernous angiomas may be found in some patients (see p. 20).

Familial cavernous hemangiomas are genetically heterogeneous. The first gene to be mapped and identified was *CCM1/KRIT1* and accounts for about 40 % of all cases (Laberge-le Couteulx et al. 1999). Subsequently two further genes were described (*CCM2/MGC4607* and *CCM3/PDCD10*) which account for about 20 and 40 % of all familial cases, respectively (Dubovsky et al. 1995; Craig et al. 1998; Riant et al. 2010). There is a significant (40–60 %) mutation detection rate in sporadic individuals with multiple lesions, and some mutation negative cases might be mosaic (Riant et al. 2010).

Meningeal hemangioma and facial nevus flammeus constitute the Sturge–Weber syndrome, and cerebral vascular lesions occur in Rendu–Osler–Weber syndrome. Although the Sturge–Weber syndrome is sometimes designated the fourth phakomatosis, there is no evidence of a genetic basis and there is no predisposition to neoplasia.

## Medulloblastoma

This tumor accounts for about 25 % of all brain tumors in children and has an incidence of approximately 1/100,000 per year. Medulloblastoma occurs predominantly in the first two decades of life, with a peak incidence between 3 and 5 years of age. Familial medulloblastoma appears to be uncommon, but has been reported in twins and siblings (Hung et al. 1990). Familial non-syndromic medulloblastoma occurs rarely (von Koch et al. 2002). Genetic disorders associated with medulloblastoma include Gorlin syndrome, familial adenomatous polyposis and Turcot syndrome, blue rubber bleb nevus syndrome, and ataxia telangiectasia (see p. 219). Gorlin syndrome is caused by germline mutations in the *PTCH* gene which encodes the sonic hedgehog receptor (see p. 252). In addition, germline and somatic mutations in another of the sonic hedgehog pathway, *SUFU* (encoding the human suppressor of fused), may be found in a subset of children with early-onset (before 3 years) medulloblastoma and can be dominantly inherited with incomplete penetrance (Taylor et al. 2002; Brugieres et al. 2010). Medulloblastoma may also occur in patients with homozygous *BRCA2* mutations (Fanconi Anaemia Type D1, see p. 249) (Offit et al. 2003; Hirsch et al. 2004).

Cancer genome analysis of medulloblastoma revealed that the most commonly altered genes were implicated in the Hedgehog, Wnt, and histone methylation pathways (Parsons et al. 2011).

## Meningioma

The most common benign brain tumor, meningioma, accounts for about 15 % of all primary brain tumors. The frequency of meningioma increases with advancing age, and it is more common in women. Multiple or familial meningioma is associated with (a) neurofibromatosis type 2 (NF2), (b) pure familial meningioma, (c) constitutional chromosome 22 rearrangements, and (d) familial schwannomatosis and *SMARCB1* mutations (see below). Meningioma also occurs with increased frequency in Werner syndrome (p. 318) and Gorlin syndrome (p. 252).

Multiple meningioma is frequent and occurs in about a third of patients with NF2 (see p. 293). Expression of NF2 is variable, so a careful search for evidence of NF2 and a detailed family history should be performed in all patients with multiple or familial meningioma, or with a young age at onset. Although many reports of familial meningioma may be variants of NF2, dominantly inherited meningioma with no evidence of NF2 does occur. However, signs of NF2 should be assiduously sought in all cases of familial meningioma as these may not be obvious. For example, Delleman et al. (1978) reported a family in which four members in two generations had meningiomas with no evidence of neurofibromatosis, but another relative had multiple meningiomas and bilateral vestibular schwannomas.

Rearrangements of chromosome 22 have been associated with meningioma: multiple tumors developed in the third decade in a mentally retarded patient with a ring chromosome 22 (breakpoints p12 and q13.3) (Arinami et al. 1986), and familial meningiomas associated with a Robertsonian chromosome 14;22 translocation have also been described. In addition, Pulst et al. (1993) reported exclusion of linkage to the NF2 kindred with familial meningioma.

Germline *SMARCB1* mutations have been identified in patients with a combination of multiple meningiomas and schwannomatosis (van den Munckhof et al. 2012). However, among a cohort of patients with multiple meningiomas and no schwannomas, germline *SMARCB1* mutations appeared to be rare (Hadfield et al. 2010) though Smith et al. (2013) described *SMARCE1* mutations in kindreds with familial spinal meningiomas with clear cell histology.

## Nerve Root Tumors

The commonest nerve root tumor is the benign schwannoma or neurolemmoma, and the most frequent site is the eighth cranial nerve (see vestibular schwannoma, p. 2). Multiple schwannomas are a feature of neurofibromatosis type 2 (NF2)

(p. 293), and schwannomas can occur in the Carney complex (p. 228), most commonly in the upper gastrointestinal tract and sympathetic nerve chains. Although familial extracranial schwannoma was initially postulated to be allelic with NF2, mutations in *SMARCB1* were demonstrated to cause autosomal dominantly inherited central and cutaneous familial schwannomas (Hulsebos et al. 2007). Subsequently *SMARCB1* mutations have been detected in about a half of familial patients and about 10 % of sporadic cases (higher in those with sporadic multiple schwannomas) (Rousseau et al. 2011; Smith et al. 2012). Although familial schwannomatosis was initially defined by the absence of vestibular schwannomas, *SMARCB1* mutations have been described in individuals with unilateral vestibular schwannomas and multiple central and cutaneous schwannomas (Smith et al. 2011). In addition, germline *SMARCB1* mutations have been reported in patients with a combination of multiple meningiomas and schwannomatosis (van den Munckhof et al. 2012). Germline mutations in *SMARCB1* can also cause rhabdoid tumor predisposition syndrome (see later), and very occasionally an *SMARCB1* mutation has been associated with both phenotypes (Eaton et al. 2011). It has been suggested that *SMARCB1* missense and splice site mutations are preferentially associated with schwannomatosis and deletions and truncating mutations with rhabdoid tumor predisposition.

## Neuroblastoma

This tumor of postganglionic sympathetic neurons is the most common solid tumor in children. Most cases are sporadic; familial cases (in which predisposition to neuroblastoma is inherited as an autosomal dominant trait) account for less than 1 % of the total. However, in a statistical analysis of the age at onset of neuroblastoma, Knudson and Strong (1972) estimated that 22 % of neuroblastomas could result from a germinal mutation and follow a “single-hit” mutation model, as in inherited retinoblastoma (Knudson 1971). The mean age at diagnosis of familial cases is 9 months (60 % at less than 1 year) compared to 30 months (25 % at less than 1 year) in nonfamilial cases (Kushner et al. 1986), and familial tumors are frequently multiple (Robertson et al. 1991).

Neuroblastoma is occasionally seen in overgrowth disorders such as Beckwith–Wiedemann syndrome and hemihypertrophy and in disorders associated with abnormal neural crest differentiation such as NF1, Hirschsprung disease, and congenital central hypoventilation syndrome. Germline mutations in *PHOX2B* were initially demonstrated in congenital central hypoventilation syndrome and subsequently in patients with neuroblastoma in association with congenital central hypoventilation syndrome and/or Hirschsprung disease and in familial non-syndromic neuroblastoma (Trochet et al. 2004). Although germline *PHOX2B* mutations may occasionally be found in patients with apparently sporadic neuroblastoma, overall it appears to be a rare cause of inherited neuroblastoma (Perri et al. 2005; McConville et al. 2006; Raabe et al. 2008).

Frequent somatic changes in neuroblastoma include *MYCN* amplification, chromosome 1p36 and 11q allele loss, and copy number gain at 17q. In addition copy number gain and activating mutations in the anaplastic lymphoma kinase (*ALK1*) proto-oncogene were found to be a common event (Chen et al. 2008; Janoueix-Lerosey et al. 2008; Mossé et al. 2008). Furthermore, germline *ALK1* mutations are an important cause of familial neuroblastoma (Janoueix-Lerosey et al. 2008; Mossé et al. 2008). Neuroblastoma susceptibility associated with *ALK1* missense mutations is inherited as an autosomal dominant trait with incomplete penetrance and often manifests with multiple tumors (Bourdeaut et al. 2012). Two *de novo* *ALK1* mutations have been associated with a novel syndrome of multifocal congenital neuroblastoma, encephalopathy, and abnormal brain stem morphology (de Pontual et al. 2011).

Genome-wide association studies have linked aggressive neuroblastoma susceptibility to common genomic variants at chromosome 6p22 and SNPs in *BARD1* (which interacts with BRCA1) (Maris et al. 2008; Capasso et al. 2009).

In familial neuroblastoma, screening by urinary catecholamine estimations from birth to age 6 years can be offered. However, although initially advocated, population screening of infants for neuroblastoma was not found to reduce mortality (Woods et al. 2002).

## Pineal Tumor

Pineal tumors account for less than 1 % of all brain tumors. A proportion of children with bilateral retinoblastoma will develop a pineal tumor (the so-called trilateral retinoblastoma). Both familial pineoblastoma and familial pinealcytoma can occur but are very rare (Peyster et al. 1986; Gempt et al. 2012). Pineoblastoma has occasionally been reported in association with familial adenomatous polyposis coli. Extragenital germ cell tumors may arise in the pineal gland and be associated with Klinefelter syndrome or 46XY gonadal dysgenesis. Pineoblastomas are also seen in carriers of *DICER1* mutations (Sabbaghian et al. 2012).

## Primitive Neuroectodermal Tumors

Cerebral primitive neuroectodermal tumors (PNETs) can occur predominantly in childhood and arise most frequently in the posterior fossa, but can occur anywhere in the brain. Medulloblastoma (see above) is the most common form of PNET, but CNS malignant rhabdoid tumors are another subset. Germline mutations in *TP53*, *PTCH* (Gorlin syndrome), and *APC* may be associated with susceptibility to central PNETs. In contrast to the peripheral type, such as Ewing sarcoma, t(11;22)(q24;q12) is uncommon in the central type.

Rhabdoid tumors are rare aggressive neoplasms that can occur in a variety of locations including the kidney, central nervous system, and soft tissues. Taylor et al. (2000)

reported a kindred with two affected relatives with a posterior fossa brain tumor in infancy (cerebellar malignant rhabdoid tumor) and posterior fossa choroids plexus carcinoma and a germline *SMARCB1* (*hSNF5*) splice site mutation. Inheritance was autosomal dominant with incomplete penetrance, and mice heterozygous for an *Snf5* deletion developed T cell lymphomas and rhabdoid tumors (Roberts et al. 2002). Germline mutations in *SMARCB1* can cause familial schwannomatosis (see above) and rhabdoid tumor predisposition syndrome. Occasionally an *SMARCB1* mutation has been associated with both phenotypes (Eaton et al. 2011). Molecular analysis of sporadic rhabdoid tumors shows evidence of *SMARCB1* inactivation in most cases, and germline *SMARCB1* mutations have been reported to be frequent in patients with such apparently sporadic rhabdoid tumors (Bourdeaut et al. 2011; Eaton et al. 2011). Thus, Bourdeaut et al. (2011) detected mutations in about a quarter of these cases, with the highest frequency in the younger children (60 % in those aged <2 years) and those with multifocal disease. Germline *SMARCB1* mutations associated with rhabdoid tumors tend to be highly penetrant, and mean age at diagnosis of rhabdoid tumor was 6 months (Bourdeaut et al. 2011). However, non-penetrance and gonadal mosaicism have been reported (Eaton et al. 2011). It has been suggested that *SMARCB1* missense and splice site mutations are preferentially associated with schwannomatosis and deletions and truncating mutations with rhabdoid tumor predisposition. *SMARCB1* is a member of the SWI/SNF chromatin-remodeling complex, and germline mutation in another member of this complex, the ATPase subunit *SMARCA4* (BRG1), was detected in two sisters with rhabdoid tumors (one brain and one renal) (Schneppenheimer et al. 2010).

Supratentorial PNETs (sPNETs) are very rare and highly aggressive embryonal tumors of the cerebrum, pineal gland, and suprasellar region. sPNETs are associated with homozygous *PMS2* mutations (De Vos et al. 2004). Other features of recessively inherited *PMS2* mutations are café-au-lait lesions and susceptibility to hematological malignancies. A family history of colorectal cancer is often absent. Homozygous recessive mutations in *BRCA2* causing Fanconi anemia subtype D1 (see p. 249) predispose to solid tumors including medulloblastoma (Offit et al. 2003; Hirsch et al. 2004).

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## Chapter 2

# Eye

The ocular tumors discussed in this section include retinoblastoma, hemangioblastoma, optic nerve glioma, meningioma, and melanoma. Ocular rhabdomyosarcoma is discussed with rhabdomyosarcoma of other sites. Genetic disorders associated with significant ocular manifestations (neoplastic and nonneoplastic) include neurofibromatosis type 1 (NF1) (p. 288), neurofibromatosis type 2 (NF2) (p. 293), von Hippel–Lindau (VHL) disease (p. 313), tuberous sclerosis (p. 307), and familial adenomatous polyposis coli (p. 241).

### Retinoblastoma

Retinoblastoma is the commonest malignant ocular tumor of childhood and affects around 1 per 20,000 children. Survival rates in the USA approach 100 % though the rates are much lower in developing countries. The tumor is derived from primitive retinal cells (retinoblasts) and usually presents in early childhood (90 % before the age of 5 years). Less than 10 % of children with retinoblastoma have a positive family history (where inheritance is autosomal dominant), but new mutations are frequent and approximately 40 % of retinoblastoma patients have a genetic predisposition. Retinoblastoma holds a unique place in human cancer genetics as the subject of Al Knudson's pioneering work on the “two-hit model of tumorigenesis” and the paradigm of the tumor suppressor gene.

Retinoblastoma typically presents as leukocoria (white eye, cat's eye reflex) or strabismus. It is bilateral in about 30 % of cases, and these children have a younger age at diagnosis (mean 8 months) than those with unilateral tumor (mean 25 months). Bilateral or multifocal tumors occur in patients with germline mutations of the retinoblastoma (*RB1*) gene, but about 15 % of children with a single tumor will have a germline mutation. The 40 % of all children with retinoblastoma who carry a germline retinoblastoma gene mutation are at risk for secondary tumors, especially osteosarcoma and soft tissue sarcomas (see below). This predisposition is exacerbated in those who receive radiotherapy. A few individuals (less

**Table 2.1** Risk of retinoblastoma in relatives of a child with retinoblastoma and no family history

Retinoblastoma in proband	Relationship to proband	Risk of carrying <i>RB</i> mutation <sup>a</sup> (%)	Risk of developing retinoblastoma tumor <sup>a</sup> (%)	Risk of developing retinoblastoma tumor <sup>b</sup> (%)
Bilateral	Offspring	50	45	44
Bilateral	Sibling or dizygotic twin	5	2.7	2
Bilateral	Offspring of unaffected sibling	0.5	0.27	
Bilateral	First cousin	0.05	0.027	
Bilateral	Monozygotic twin	100	90	
Unilateral	Offspring	7.5	5.7	1
Unilateral	Sibling or dizygotic twin	0.8	0.4	1
Unilateral	Offspring of unaffected sibling	0.08	0.04	
Unilateral	First cousin	0.008	0.004	
Unilateral	Monozygotic twin	10	5.4	

<sup>a</sup>The calculated risks from Musarella and Gallie (1987) take into account the retinoblastoma mutation rate and assume that 90 % of individuals with a germline mutation will develop a tumor and 15 % of patients with unilateral retinoblastoma have a germline mutation

<sup>b</sup>The risks from Draper et al. (1992) for siblings relate to the first child, when there are further unaffected siblings the risk will be lower

than 2 %) with germline retinoblastoma gene mutations may develop a retinoma. These benign retinal lesions appear as focal translucencies with cottage-cheese-like calcification and underlying choroidal and retinal pigment epithelial disturbance. A retinoma is thought to result when a second *RB1* mutation occurs in a retinoblast which is almost differentiated. About 2 % of all patients with retinoblastoma also have an intracranial lesion, usually in the pineal gland. The association of pineal tumor and retinoblastoma is often termed trilateral retinoblastoma and occurs in patients with germline retinoblastoma mutations.

The retinoblastoma mutation is non-penetrant in approximately 10 % of obligate carriers. Although there is no detectable paternal age effect on new mutations for retinoblastoma, most new hereditary mutations develop in paternal germ cells (Zhu et al. 1989). An excess of males among patients with bilateral sporadic disease has been noted, and Naumova and Sapienza (1994) suggested the involvement of genomic imprinting effects. Although an excess of retinoblastoma cases was reported in a Netherlands cohort of children conceived by assisted reproductive technologies, this finding requires replication (Moll et al. 2003).

About 60 % of retinoblastomas result from somatic (acquired) mutations inactivating both alleles of the retinoblastoma gene. Such patients develop single tumors and there is no risk to their offspring. However, 15 % of patients with single tumors will have a germline mutation. Risk estimates for the relatives of isolated cases of retinoblastoma are given in Table 2.1. The later estimates of Draper et al. (1992) are lower in some cases than earlier estimates. Genetic counseling for the relatives of patients with

isolated unilateral retinoblastoma is complicated by the possibility for mosaicism of a germline *RB1* mutation (Lohmann et al. 1997). Individuals with genetic retinoblastoma (germline mutation) are at increased risk for second tumors, but children with nongenetic tumors are not. The risk of second primary neoplasms reflects a genetic predisposition to non-retinoblastoma tumors and the effects of treatment (e.g., radiation). Draper et al. (1986) estimated that the cumulative probability of a second primary neoplasm in genetic retinoblastoma patients at 18 years after diagnosis is 8.4 % for all tumors and 6 % for osteosarcoma. The risks for osteosarcoma outside and within the radiation fields were 2.2 and 3.7 %, respectively, and thus patients with genetic retinoblastoma may be more sensitive to radiation-induced oncogenesis. The most common site of osteosarcoma outside the radiation field is in the femur, and genetic retinoblastoma patients are at a 200–500-fold increased risk of this complication. Soft tissue sarcomas also occur with increased frequency in patients with genetic retinoblastoma. Studies of non-ocular cancer in relatives of retinoblastoma patients have demonstrated that retinoblastoma mutation carriers are at increased risk of a variety of other cancers (overall relative risk 11.6) including cancer of the lung (relative risk 15), malignant melanoma, and bladder cancer (Sanders et al. 1988). Moll et al. (1996) estimated cumulative incidences of second primary tumors in hereditary retinoblastoma of 4 and 18 % at ages 10 and 35 years, respectively. Eng et al. (1993) reported a cumulative probability of death from a second primary neoplasm of 26 % at 40 years after bilateral retinoblastoma. The most common second primary tumors were bone and connective tissue neoplasms and malignant melanoma. Eng et al. (1993) also demonstrated that radiotherapy increased the risk of a second primary tumor and suggested that all patients with inherited retinoblastoma should receive lifelong surveillance for second primary tumors. In a follow-up study of UK hereditary retinoblastoma cases, Fletcher et al. (2004) found a cumulative cancer incidence and mortality of 69 and 48 %, respectively. In contrast to patients treated by radiotherapy, sarcomas accounted for only a minority of tumors, and there was an increased mortality for lung cancer (standardized mortality ratio (SMR) = 7), bladder cancer (SMR = 26), and all other epithelial cancers combined (SMR = 3.3).

The retinoblastoma gene was initially assigned to chromosome 13 band q14 by reports of children with retinoblastoma and interstitial deletions of chromosome 13. About 3 % of children with retinoblastoma will have a cytogenetically visible chromosome 13 deletion or translocation. Retinoblastoma cases with constitutional chromosome deletion may have associated mental retardation, and most have reduced serum levels of esterase D (the gene for which maps close to the retinoblastoma gene (*RB1*)). The *RB1* gene spans 200 kb in 13q14 (Friend et al. 1986) and encodes a 110-kDa nuclear phosphoprotein with tumor suppressor activity (Huang et al. 1988).

The identification of the retinoblastoma gene has enabled the presymptomatic identification of individuals with germline mutations by a variety of techniques. Intragenic restriction fragment length polymorphisms (RFLPs) are informative in about 95 % of families and usually allow accurate presymptomatic diagnosis of at-risk relatives in families with two or more affected members but are unhelpful in families with only a single case (Wiggs et al. 1988). Mutation detection rates of

80 % or more were reported by Lohmann et al. (1996) and Houdayer et al. (2004) using a variety of molecular genetic techniques. Germline deletions are not infrequent, and an appropriate deletion scanning approach (e.g., multiplex ligation-dependent probe amplification (MLPA)) should be performed as part of the mutation detection strategy. *RB1* mutations are heterogeneous, and generally no clear genotype–phenotype associations have been described except that promoter mutations and some intragenic mutations with residual protein activity may display reduced penetrance (Kratzke et al. 1994; Cowell et al. 1996). The identification of a germline mutation in a unilateral sporadic case distinguishes those individuals with simplex retinoblastoma and a new germline mutation from nonhereditary cases. When a germline mutation is identified, other relatives can be tested. When histopathological material (formalin fixed paraffin embedded) from a deceased patient is available, mutation analysis can be undertaken on the tumor tissue and further investigations undertaken to determine if a characterized mutation is somatic or germline. Indeed, if tumor tissue is available, then this will be analyzed first to define the two *RB1* mutations. Constitutional DNA (e.g., blood) is then tested to determine if both are somatic or one is germline (as mosaicism is not uncommon, blood DNA testing must use methods sensitive enough to detect mosaic mutations). If two mutations are detected in the tumor and neither is detected in blood, then siblings do not require surveillance though there will still be a small risk to the patient's offspring (from mosaicism). A pathogenic mutation can be detected in blood DNA of ~95 % of patients with hereditary retinoblastoma. In patients who present with developmental delay and/or dysmorphic features, FISH or array CGH analysis to detect copy number variations is performed first.

Children with an *RB1* mutation should undergo an eye examination every 3–4 weeks until age 1 year and then every 2–3 months until age 5 years followed by annual examination for the rest of their lives (Lohmann et al. 2011). There are no specific guidelines for the detection of non-ocular second tumors, but complaints of bone pain or lumps should be investigated promptly.

In the absence of molecular genetic diagnosis, the parents and siblings of all children with retinoblastoma should undergo thorough ophthalmological assessment. Offspring and siblings of retinoblastoma patients should be followed up from birth, with complete retinal examination. For example, examination should be performed at birth and monthly until 3 months of age without anesthesia, then under general anesthetic every 3 months until the age of 2 years, then every 4 months until the age of 3 years. Thereafter, examinations without general anesthesia can be performed every 6 months until the age of 5 years, and then every 12 months until the age of 11 years (although the frequency and duration of screening can be modified according to the results of DNA analysis). Parents of children with apparently sporadic retinoblastoma must be examined to exclude a regressed tumor or retinoma because this would identify the child as having a germline *RB1* gene mutation. Children with retinoblastoma will require careful follow-up to detect new tumors or recurrence. New tumors occurred in 11 % of children studied by Salmonsens et al. (1979). Traditionally, all children with retinoblastoma are followed up with regular retinal examinations under general anesthesia. However, the application of DNA

techniques to identify *RB1* gene mutations in tumors and constitutional DNA enables follow-up to be restricted to those shown to have germline *RB1* mutations. This not only enhances management of at-risk relatives but is also a cost-effective strategy (Noorani et al. 1996). Survivors of bilateral retinoblastoma (and unilateral retinoblastoma in those with germline retinoblastoma gene mutations) are at high risk of osteosarcoma in adolescence and of the occurrence of other cancers (see above).

## Retinal Astrocytic Hamartoma

This benign, nonprogressive tumor is most commonly seen in patients with tuberous sclerosis and occurs in about 50 % of patients with this disorder. Retinal astrocytic hamartomas have also been described rarely in neurofibromatosis type 1 and type 2 (see p. 288 and p. 293) (Sachdeva et al. 2010; Martin et al. 2010). Sporadic retinal astrocytomas differ from those in tuberous sclerosis in that a proportion appear to be true neoplasms and may invade locally (Arnold et al. 1985).

## Optic Glioma

Although rare, glioma is the commonest optic nerve tumor in childhood. Optic glioma is associated with neurofibromatosis type 1 (NF1) (see p. 288) in a third of cases. Approximately 15 % of patients with NF1 develop an optic glioma (which may be bilateral) though the frequency of symptomatic optic glioma is about 5 % (Lewis et al. 1984; Huson et al. 1988; Singhal et al. 2002). McGaughan et al. (1999) estimated an actuarial risk of optic glioma in NF1 patients of 3.7 % at age 10 years and 6.2 % at age 25 years. A potential association between mutations at the 5' end of the *NF1* gene and the development of optic nerve gliomas has been reported (Sharif et al. 2011).

All patients with optic glioma, and their families, should be assessed for evidence of NF1. Histological appearance is of a low-grade (pilocytic) astrocytoma, spontaneous regression may occur, and many consider these tumors to be congenital hamartomas rather than acquired neoplasms (Riccardi and Eichner 1986). Optic gliomas usually originate in the optic nerves or chiasm, and presentation is usually with visual impairment and/or painless proptosis. Most NF1-associated optic gliomas are orbital. Computerized tomography (CT) or magnetic resonance image (MRI) scanning will demonstrate optic glioma and differentiate from optic nerve meningioma. The natural history of optic glioma is not well defined. Most are nonprogressive and conservative management is usually preferred. Treatment (surgery or radiotherapy) of optic nerve glioma is indicated for progressive visual loss associated with proptosis. Treatment of chiasmal lesions is more difficult, but again, most are nonprogressive and conservative management is pursued.

## Ocular Choristoma

Ocular choristomas are congenital lesions, which are deposits of normal tissue in an abnormal location. They are the most common epibulbar and orbital tumors in children, with an incidence of about 1 per 5,000 (Mansour et al. 1989). Dermoid and epidermoid cysts are both included in this group. Ocular choristomas may be associated with Goldenhar syndrome (hemifacial microsomia) or epidermal nevus syndrome. In the latter disorder, choristomas are frequently bilateral and extensive. Goldenhar syndrome is usually sporadic but in rare cases can be familial (Tasse et al. 2007). Familial choristoma with dominant inheritance not associated with Goldenhar syndrome occurs rarely (Mansour et al. 1989).

## Ciliary Body Medulloepithelioma

These very rare eye tumors have been reported to occur in children with DICER1 mutations (Slade et al. 2011).

## Cavernous Hemangioma

This rare ocular tumor should be distinguished from retinal hemangioblastoma. Mean age at diagnosis is 23 years and less than 10 % are bilateral. Cavernous hemangioma is usually nonprogressive, and serious complications are uncommon. Retinal or optic disc cavernous hemangiomas are associated with cutaneous vascular lesions in about 28 % of patients and in some patients with intracranial cavernous hemangioma (Lewis et al. 1975). A triad of ocular, central nervous system, and cutaneous cavernous hemangiomas can be dominantly inherited with variable expression and incomplete penetrance (Brown and Shields 1985). Thus, the finding of retinal cavernous or choroidal hemangioma is an indication to search for features of systemic or familial disease (Sarraf et al. 2000). It has been estimated that about 5 % of patients with cerebral cavernous hemangiomas will have a retinal lesion (Labauge et al. 2006). Familial cerebral cavernous hemangioma (p. 5) is a genetically heterogeneous disorder and can be caused by mutations in *KRT1* (*CCM1*), *CCM2*, or *PDCD10* (*CCM3*), and it appears that each of these subtypes may be associated with retinal lesions (Labauge et al. 2006).

## Hemangioblastoma

Retinal hemangioblastoma (also called angioma) is the most common presentation of von Hippel–Lindau (VHL) disease (Maher et al. 1990). The exact proportion of patients with retinal hemangioblastoma who have this disease is unclear. The most frequent estimate is 40 %, but Neumann and Wiestler (1991) detected evidence of

**Table 2.2** Estimated probability of underlying VHL disease in a patient with a solitary ocular angioma after careful ophthalmic screening

	Probability by age group (years)			
	<20	21–40	41–60	>60
Other negative information				
None	0.30	0.30	0.30	0.30
DNA	0.11	0.11	0.11	0.11
Systemic screening	0.27	0.13	0.06	0.02
Parent history	0.19	0.13	0.09	0.09
Parent history + systemic screening	0.17	0.05	0.02	0.01
DNA + parent history	0.06	0.04	0.03	0.03
DNA + systemic screening	0.10	0.04	0.02	0.01
DNA + systemic screening + parent history	0.06	0.01	0.00	0.00

Source: From Webster et al. (2000) – J Med Genet. 37:62–3

the disease in 86 % of their patients with retinal angiomas. All patients with retinal angioma should be investigated for subclinical manifestations of VHL disease (see p. 313). All patients with multiple retinal angiomas satisfy clinical diagnostic criteria for VHL disease, but in atypical cases, expert ophthalmological review is helpful to confirm that the lesions are hemangioblastomas and not other types of vascular lesion (e.g., Coat disease). Webster et al. (1998) investigated 17 cases with VHL-like solitary ocular angioma and found no evidence of other complications of this disease in themselves or in family members. They concluded that sporadic ocular angioma can occur in the absence of VHL disease. The tumors are similar in anatomical location, and cases are similar in age of presentation and degree of visual morbidity compared to those with the disease. Overall the risk of underlying VHL disease in a patient with a solitary ocular angioma was 30 %; this risk decreased with negative DNA and clinical screening and also with increasing age (Table 2.2) (Webster et al. 1999).

Histologically VHL-associated retinal hemangioblastomas resemble cerebellar hemangioblastomas with stromal cells surrounding capillary endothelial cells and glial cell admixed. Molecular studies demonstrate that loss of the wild-type VHL allele occurs in the stromal cells, and this leads to activation of HIF transcription factors and expression of vascular endothelial growth factor and other angiogenic factors (Chan et al. 2007).

## Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, with an incidence 6/million per year (lifetime risk 1 in 2,500) (Canning and Hungerford 1988). Familial cases are uncommon and account for about 0.6 % of all patients (Singh et al. 1996). Canning and Hungerford (1988) reviewed 14 kindreds with familial ocular melanoma. The mean age at diagnosis is significantly younger in familial than in sporadic cases (42 and 56 years, respectively), and inheritance can be autosomal dominant with incomplete penetrance. Intraocular melanoma may



be associated with familial atypical mole-melanoma syndrome (p. 178), ocular melanocytosis, and neurofibromatosis type 1 (p. 288) (Singh et al. 1995). Though a few studies have suggested that uveal melanoma might be linked to breast cancer (in particular *BRCA2* mutations), this link does not appear to be a frequent cause of uveal melanoma (Harbour 2012).

The most commonly detected somatic mutations in uveal melanoma are missense mutations in *GNAQ* or *GNA11* genes (~80 % of cases) and inactivating mutations in *BAP1* (~50 % of cases) (van Raamsdonk et al. 2010; Harbour et al. 2010). Germline *BAP1* mutations can predispose to a multiple system-inherited cancer syndrome characterized by susceptibility to uveal melanoma and other tumors including cutaneous melanocytic tumors, malignant mesothelioma, lung adenocarcinoma, and abdominal adenocarcinoma (Testa et al. 2011; Abdel-Rahman et al. 2011). Familial uveal melanoma is now thought to account for 2–5 % of all cases (Harbour 2012).

## Meningioma

Intraorbital meningioma is an uncommon tumor that may present at any age but predominantly occurs in middle-aged women. Most tumors are unilateral, but a small proportion of patients have bilateral involvement. Optic nerve sheath meningioma may complicate NF2 (see p. 293), when it is usually unilateral but can be bilateral (Jain et al. 2010).

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## Chapter 3

# Cardiorespiratory System and Thorax

### Head and Neck Cancer

#### *General*

Squamous carcinomas of the head and neck (a grouping which includes tongue and mouth, nasopharynx, and larynx) are associated with cigarette smoking and alcohol ingestion (although the risk factors for different sites may differ). In addition, infection with human papillomavirus (HPV) is associated with cancers of the oropharynx (D'Souza et al. 2007). Specific head and neck cancers may be associated with familial cancer syndromes such as hereditary non-polyposis colon cancer syndrome and Li–Fraumeni syndrome (larynx) and Fanconi anemia (oral cancer). Foulkes et al. (1996) reported a relative risk of 3.7 for developing head and neck cancer in first-degree relatives of an affected case, but the relative risk was almost 8 if the index case had multiple primaries.

Exome resequencing studies of squamous carcinomas of the head and neck revealed that the most frequently mutated genes were *TP53*, *NOTCH1*, *CDKN2A*, *PIK3CA*, *FBXW7*, *IRF6*, *PTEN*, and *HRAS* (Agrawal et al. 2011; Stransky et al. 2011) and that HPV-associated cancers had a lower overall number of mutations per tumor. *TP53* mutations were not detected in HPV-associated tumors but were present in ~80 % of HPV-negative tumors (Agrawal et al. 2011). Overall, it was noteworthy that although head and neck squamous carcinomas are clinically categorized by anatomical location, at a molecular level the presence of *TP53* inactivation (through somatic mutation or HPV infection) appears to be a common feature (Stransky et al. 2011).

## ***Specific Sites***

### **Nasopharynx**

Cancers of the nasopharynx account for 0.1 % of all cancers and differ from tumors in other parts of the pharynx by not being associated with tobacco or alcohol. There is a high incidence (lifetime risk 1.6 %) of nasopharyngeal carcinoma among the southern Chinese (100-fold higher than that of European populations), and both environmental (high dietary intake of salted fish and, particularly, Epstein–Barr virus, EBV) and genetic factors have been implicated. Familial clustering of nasopharyngeal carcinoma is well recognized (Zeng and Jia 2002).

Using meta-analysis, Burt et al. (1996) also demonstrated a significant association with HLA types in non-Chinese populations. This work has been followed up by more detailed studies, and *HLA-A* has been consistently shown to be associated with nasopharyngeal carcinoma susceptibility (Lu et al. 2005). A genome-wide association study confirmed the role of HLA and also identified novel associations at *MDS1-EVII* (3q26), *CDKN2A/CDKN2B* (9p21), and *TNFRSF19* (13q12), implicating the TGF- $\beta$  and JNK signaling pathways in susceptibility to nasopharyngeal carcinoma (Bei et al. 2010).

### **Larynx**

Cancers of the larynx account for 1 % of all cancers and are associated with tobacco smoking and alcohol. Carcinoma of the larynx has been reported in families with HNPCC (Lynch syndrome) (p. 65), *BRCA2* mutations (p. 91), and in Muir–Torre (p. 286) and Li–Fraumeni syndromes (p. 271).

### **Tumors of the Thymus**

Thymomas are rare tumors of the thymic epithelium that usually occur in adults (average age at onset of 48 years) and are usually sporadic. About 65 % are benign, but when they occur in children, they are more likely to be malignant. Familial occurrence is rare, but a sibship has been described in which two of three siblings died of thymoma (Matani and Dristas 1973). Malignant epithelial tumors of the thymus (thymic carcinoma and thymoma) have also been described in two members of a sibship (Wick et al. 1982). Nicodème et al. (2005) described a family harboring a constitutional translocation t(14;20)(q24;p12) in which 3 of 11 translocation carriers developed a thymoma (*RAD51L* and *BMP2* were suggested as candidate genes).

Other tumors that may involve the thymus are carcinoids, germ cell tumors, neurogenic tumors, thymolipomas, and Hodgkin disease. About one-third of thymic carcinoids are associated with multiple endocrine neoplasia type 1 (MEN 1) (see p. 278). A possible genotype–phenotype association between thymic carcinoids and truncating *MEN1* mutations has been reported (Lim et al. 2006).

## Tumors of the Lung

Lung (bronchial) cancer accounts for 14 % of all new cases of cancer in males and 11 % in females. The two most common histological types of lung cancer (small cell and squamous) are known to be strongly related to cigarette smoking. It is estimated that 90 % of lung cancer in males and 85 % in females is attributable to cigarette smoking. Adenocarcinoma (moderately associated with smoking) and alveolar cell carcinoma (not associated with smoking) account for 10 % of all lung cancer. In addition to smoking, other environmental agents such as asbestos, radiation, and air pollution have been associated with lung cancer. The most frequent somatic events in lung cancer are inactivation of *TP53* and mutations in *KRAS* or *EGFR* mutations (mainly in adenocarcinoma) and alterations in the *CDKN2A/ARF/RB1* pathway (Brennan et al. 2011).

Familial clustering of lung cancer occurs, but as relatives of lung cancer patients are more likely than average to be smokers or passive smokers, careful studies are required to distinguish the effects of shared environment (e.g., asbestos exposure) and lifestyle (e.g., smoking) from that of genetic predisposition. Although studies of the familial incidence of smoking-related lung cancer should be interpreted cautiously, there is evidence for an increased risk of lung cancer among relatives of affected patients. Sellers et al. (1990) performed segregation analysis which allowed for variable age at onset and smoking history in affected patients. They concluded that familial clustering of lung cancer was consistent with Mendelian codominant inheritance of a rare autosomal gene with variable age at onset. It was estimated that at age 50 years, 69 % of lung cancer resulted from genetic factors acting in combination with smoking, but that at age 70 years, 72 % of lung cancer could be attributed to environmental factors alone. In a subsequent analysis, Sellers et al. (1994) provided further evidence that Mendelian factors may influence the occurrence of smoking-related cancers in the relatives of lung cancer probands. Schwartz et al. (1996) analyzed the family histories of nonsmokers with lung cancer and found a 7.2-fold increased risk of lung cancer in the first-degree relatives of nonsmokers who developed lung cancer aged 40–59 years. Risk of lung cancer was also increased in the offspring of nonsmoking cases. These findings suggest that a subset of relatives of early-onset, nonsmoking lung cancer cases is at increased genetic risk, and genetic factors have been particularly linked to early-onset cases (Cassidy et al. 2006).

Candidate gene lung cancer susceptibility studies have generally not been replicated by genome-wide association studies, though glutathione S transferase M1 (*GSTM1*) genotype has been associated with lung cancer risk in a meta-analysis, and the I157T *CHEK2* variant that has been reported to predispose to breast cancer has also been associated with a reduced risk of lung cancer (Brennan et al. 2011).

Genome-wide association studies have repeatedly demonstrated an association between lung cancer risk and common variants in the *CHRNA5-CHRNA3-CHRNA4* nicotinic acetylcholine receptor subunit gene cluster on chromosome 15q25 (relative risk ~1.3). However, it was unclear whether the association was direct or whether the link was indirect via susceptibility to cigarette smoking though recent data suggests the latter option (Wang et al. 2011). A locus for familial lung cancer susceptibility

has been mapped to 6q23-25 and *RGS17* suggested as the possible candidate gene responsible (You et al. 2009). A *TERT* SNP histology on chromosome 5p15.33 has been associated with lung adenocarcinoma risk but not with other histologies (Landi et al. 2009). However, it has been estimated that <10 % of the familial risk of lung cancer can be explained by the susceptibility loci at 15q25, 5p14, and 6p21 (Brennan et al. 2011). The role of rare variants in lung cancer susceptibility remains to be fully investigated, but a germline *EGFR* variant (T790M) was detected in a family with multiple cases of non-small cell lung cancer (Bell et al. 2005). For a discussion of the genetics of the rare pediatric lung tumor pleuropulmonary blastoma, see page 294.

## Mesothelioma

This cancer arises from the mesothelial cells that line the pleural, pericardial, and peritoneal surfaces. Although classically associated with asbestos exposure, familial clusters of mesothelioma may occur suggesting that genetic factors may influence susceptibility (Carbone et al. 2007). Testa et al. (2011) demonstrated that germline mutations in *BAP1* predisposed to mesothelioma, uveal melanoma (see p. 21), and possibly other cancer types, and it has been suggested that the occurrence of mesothelioma and melanoma in *BAP1* mutation carriers may depend on exposure to asbestosis and sunlight. The relative frequency of peritoneal to pleural mesothelioma appears to increase in inherited cases compared to sporadic cases.

## Cardiac Tumors

Primary cardiac tumors are rare, being found in less than 0.1 % of autopsies. The most common tumor is myxoma, which accounts for up to 50 % of the total. Most myxomas are sporadic and occur in the over-50 years age group. However, familial myxoma has been described and may occur as a dominant trait. Familial myxomas are more frequently multiple and have an earlier age at diagnosis (20–40 years) than in sporadic cases.

Cardiac myxomas occur in the autosomal dominantly inherited Carney complex type 1 (NAME syndrome (Carney complex); p. 228), which is characterized by the occurrence of cardiac myxoma, spotty pigmentation and cutaneous myxomas, and pituitary and adrenocortical tumors (Carney 1995). Cardiac myxoma is the most serious complication of Carney complex, and all individuals at risk for familial cardiac myxoma should be screened regularly by echocardiography. Carney complex type 1 is caused by mutations in the protein kinase A regulatory subunit-1- $\alpha$  gene (*PRKARIA*), and mutations in *PRKARIA* have been described in familial cardiac myxoma without other features of Carney complex type 1 (Kirschner et al. 2000).

Cardiac rhabdomyomas are rare and most affected patients have tuberous sclerosis (see Part Three). These are usually asymptomatic, are most frequent in infants, and often involute with age.



Cardiac fibromas are a feature of Gorlin syndrome (p. 246), although they occur in only a small proportion (approximately 3 %) of patients with this disorder (Gorlin 1987, 1995).

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## Chapter 4

# Endocrine System

### Thyroid Tumors

The incidence of primary epithelial cancer of the thyroid is 0.7 per 100,000 in males and 1.9 per 100,000 in females in the UK. Overall, the annual incidence of thyroid cancer is between 0.9 and 5.2 per 100,000 people, with a ratio of women to men of 2–3:1. Thyroid cancer is the most rapidly rising incident cancer in women and the second most rapidly rising incident cancer in men in the USA. Whether the papillary or follicular histology is favored is dependent on the amount of dietary iodine in a particular region. Papillary thyroid carcinoma (PTC) accounts for more than 50 % of cases in the UK and USA, the next most common type of thyroid cancer being follicular thyroid carcinoma (FTC). Less frequent types are medullary thyroid carcinomas (MTC), anaplastic (undifferentiated) carcinomas, Hürthle cell carcinomas, and squamous cell carcinomas. Other non-epithelial malignancies that may be observed in the thyroid include lymphomas and sarcomas, but these are rare.

#### *Papillary Thyroid Carcinoma (PTC)*

Genetic susceptibility to PTC can be seen in familial adenomatous polyposis syndrome (FAP), Cowden syndrome (CS), possibly Carney complex (CNC), and in a familial site-specific syndrome. These syndromes are described in detail in the next section. Thyroid cancers can be detected in 2–25 % of FAP patients. It should be noted that there is evidence that what is commonly referred to as “PTC” in FAP is not identical to classic PTC (cPTC) nor its follicular variant of PTC (FvPTC). FAP-related thyroid cancer is of a distinct cribriform subtype, currently referred to as cribriform-morular variant (cmv) of PTC (Harach et al. 1994; Ito et al. 2011). In contrast to classic PTC, FAP-related thyroid cancers do not show the typical fir tree branching papillary pattern, and psammoma bodies are rare or nonexistent. This distinct architecture seen in APC-related thyroid carcinomas is very unusual in sporadic PTC (Harach et al. 1994). FAP-related cmv-PTC is often multifocal

**Table 4.1** Familial PTC

Syndrome	Chromosomal location	Comments
PTC with cell oxyphilia	TCO, 19p13.2	Oncocytic PTC
PTC without oxyphilia	19p13.2	
Multinodular goiter (MNG)	MNG1, 14q31	MNG and PTC
	MNG2, Xp22	MNG only
PTC and renal tumors	1q21	PTC, thyroid nodular disease, papillary renal cell carcinoma
PTC and clear cell renal cancer	t(3;8)(p14.2;q24.1)	
FNMTc	NMTC1, 2q21	Follicular variant of PTC

Reviewed in Eng (2000a, b, c)

compared to the rare sporadic cmv-PTC (Ito et al. 2011). Recent studies suggest that FAP-related cmv-PTC patients are predominantly female, and the great majority of the germline *APC* mutations occurred in exon 15, especially the 5' portion of this exon (Cetta et al. 2000; Jarrar et al. 2011). Unlike the general population, PTC is underrepresented in CS-related thyroid carcinomas, especially in those with germline *PTEN* mutations (Harach et al. 1999). In contrast, however, pilot data suggest that PTC is overrepresented in individuals with CS who carry germline *SDHB/SDHD* variants of germline *KLLN* epimutation compared to those with germline *PTEN* mutations (Ni et al. 2008; Bennett et al. 2010). While thyroid tumors, for example, PTC, have been reported in CNC, it is currently unclear if PTC are true component cancers of CNC.

Several putative loci, but no genes, have been identified for non-syndromic familial PTC and are summarized in the Table 4.1. It is believed that the 14q31-related multinodular goiter gene is *DICER1* although it is unclear whether PTC is part of this newly described syndrome that most likely comprises multinodular goiter, Sertoli-Leydig cell tumor, and perhaps Wilms' tumor (Rio Frio et al. 2011). Previously, *DICER1* germline mutations are associated with the rare phenotypes of pleuropulmonary blastoma and familial cystic nephroma. Various low-penetrance germline variants, notably in pre-miR-146a (odds ratio=1.6), have been reported (Jadzewski et al. 2009).

Sporadic PTC are characterized by somatic translocations between one of several genes and the intracellular domain of RET (at intron 11) termed RET/PTCn. The precise frequency is unknown but could range from 10 to 60 %. Typically, the 5'-translocation partner encodes a protein which can force dimerization of the kinase domain of RET, for example, leucine zippers (Lanzi et al. 1992; Sozzi et al. 1992; Bongarzone et al. 1993). It would appear that PTC tumors without RET/PTC translocations harbor a relatively high frequency of somatic gain-of-function *BRAF* mutations (Kimura et al. 2003; Soares et al. 2003). As somatic *BRAF* mutations and the presence of the RET/PTC translocation or *RAS* mutations are mutually exclusive, it is suggested that activation of the RAS-RAF-MAP kinase pathway is important in PTC development but that two insults to this pathway are not necessary.

## ***Follicular Thyroid Carcinoma (FTC)***

FTC is a proven component cancer in *PTEN*-related CS and Werner syndrome. In germline *PTEN* mutation-positive CS, FTC is the major component of thyroid cancer (Harach et al. 1999; Ni et al. 2008; Bennett et al. 2010). However, rarely, PTC and the follicular variant of PTC are also observed (Marsh et al. 1998). In Werner syndrome, thyroid carcinoma, mainly FTC, is more commonly observed in Japanese patients than those from elsewhere. Both syndromes are discussed in detail in the next section.

The molecular etiology of sporadic FTC remains unknown. A publication reporting a high frequency (50 %) of somatic *PAX8/PPARG* translocations in FTC initially suggested that this was the initiating event (Kroll et al. 2000). Subsequently, the frequency of this *PAX8/PPARG* translocation, which inactivates *PPARG* by a dominant negative mechanism, was found to be much less (10 %) in sporadic FTC (Aldred et al. 2003). Instead, loss of function by a haploinsufficient mechanism seems to occur more frequently and plays some role in FTC development (Aldred et al. 2003). Microarray expression strategies have been used to attempt to elucidate the molecular pathogenesis of sporadic FTC (Aldred et al. 2003).

## ***Medullary Thyroid Carcinoma (MTC)***

MTC, which is a carcinoma of the parafollicular C cells, is a proven component cancer of multiple endocrine neoplasia type 2 (MEN 2), caused by germline mutations in the *RET* proto-oncogene. This syndrome is detailed in the next section. While C cell hyperplasia was believed to be pathognomonic for MEN 2, once *RET* was identified as the MEN 2 susceptibility gene, it was discovered that this association no longer holds true, and indeed C cell hyperplasia can be found in truly sporadic MTC (Eng et al. 1995a, b; Marsh et al. 1996b).

The etiology of sporadic MTC is also not well known. Among all presentations of MTC, clinical epidemiological studies have shown that 25 % can be attributable to MEN 2. Occult germline mutations in the *RET* proto-oncogene can be found in 5–15 % of apparently sporadic MTC, that is, without obvious syndromic features or family history (Blaugrund et al. 1994; Eng et al. 1995a, b; Wohlik et al. 1996; Schuffenecker et al. 1997). Due to these accumulating data, the general recommendations, such as from the American Thyroid Association Management Guidelines, are to offer *RET* mutation analysis to all presentations of MTC regardless of age, presence of syndromic features, or family history (Kloos et al. 2009).

Somatic *RET* mutations have been reported to occur in 10–80 % of sporadic MTC (Eng et al. 1994, 1995a, b; Hofstra et al. 1994; Marsh et al. 1996a). The great majority of somatic *RET* mutations are M918T. Of note, somatic mutations have been found to occur in patches or subpopulations even within a single tumor (Eng et al. 1996a, b, 1998). Up to 80 % of sporadic MTC harbor at least one subpopulation with somatic

M918T mutation (Eng et al. 1996a, b). It remains controversial whether somatic M918T in the primary tumor portends a poor prognosis. Unfortunately, because some studies have used mixed primary and metastatic tumors (e.g., Schilling et al. 2001), and because of the presence of subpopulations and the varied mutation detection technologies employed, whether M918T status is associated with prognosis remains unknown. Nonetheless, one well-designed study did not show a difference in clinical outcome with or without somatic M918T (Marsh et al. 1996b). In general, MEN 2-associated MTC do not carry somatic intragenic *RET* mutation as a second genetic event (Eng et al. 1995a, b). However, there are rare instances of somatic M918T occurring in MEN 2-associated MTC (Marsh et al. 1996a). It is also believed that duplication of the mutated *RET* allele in MEN 2A-associated MTC may contribute to carcinogenesis (Koch et al. 2001). A recent study of a relatively small series of sporadic MTC found that half of all somatic *RET* mutation-negative MTC harbored somatic mutations in *HRAS*, but not in other *RAS* family members (Moura et al. 2011).

### ***Benign Neoplasia of the Thyroid***

Benign thyroid neoplasia such as follicular adenomas, multinodular goiters, and hamartomas are components of CS (see below). Due to the risk of recurrence and the risk of thyroid cancer in CS patients or in those with a proven germline *PTEN* mutation, a total thyroidectomy should be performed if surgery is being considered for these benign thyroid lesions. Germline *DICER1* mutations have been described in individuals and families with multinodular goiter, usually accompanied by other features noted above and in the next chapter. At least in one study, benign thyroid nodules appear to be relatively common in individuals with FAP, although malignant disease was prevalent only in ~3 % (Jarrar et al. 2011).

### **Parathyroid Tumors**

Parathyroid neoplasias are very common; however, familial hyperparathyroidism occurs at a frequency of about 0.14 per 10,000 and, for the most part, occurs as part of the multiple endocrine neoplasia syndromes (MEN; see p. 278 and 281), with chief cell hyperplasia as the usual histological change. The genetic differential diagnosis of parathyroid hyperplasia or parathyroid adenoma includes MEN 1, caused by germline *MEN1* mutations; MEN 2, caused by germline *RET* mutations; and hyperparathyroidism–jaw tumor syndrome (HPT-JT), caused by germline mutations in *HRPT2*. Familial site-specific hyperparathyroidism can be caused by germline *MEN1* mutations as well as due to HPT-JT (Teh et al. 1996; Kassem et al. 2000). Germline mutations in the calcium-sensing receptor gene have been identified in benign familial hypocalciuric hypercalcemia and, in homozygous form, cause neonatal severe hyperparathyroidism with parathyroid hyperplasia (Pollak et al. 1993). While parathyroid disease is very common in MEN 1 and often the first

component neoplasia to manifest, hyperparathyroidism in MEN 2 occurs in 15–30 % of MEN 2A cases and likely manifests relatively later in life (Schuffenecker et al. 1998). Germline *RET* C634R is particularly associated with the development of hyperparathyroidism in MEN 2A (Mulligan et al. 1994; Eng et al. 1996a, b).

Parathyroid carcinoma is extremely rare, but it is an important component neoplasia of HPT-JT (Carpten et al. 2002). It is unclear, however, whether parathyroid carcinoma is a true component cancer of MEN 1 as well, but it does not appear to be so.

Somatic loss of heterozygosity (LOH) of markers on 11q13 and somatic *MEN1* mutations have been described in parathyroid hyperplasias (Friedman et al. 1992). Somatic mutations in *HRPT2* occur with a relatively high frequency in sporadic parathyroid carcinomas (Howell et al. 2003; Shattuck et al. 2003). Surprisingly, occult germline mutations in *HRPT2* were found in 3 of the 15 apparently sporadic patients with parathyroid carcinoma (Shattuck et al. 2003).

Those at risk for parathyroid hyperplasia and/or adenoma should undergo routine clinical surveillance. Management for parathyroid disease for MEN 2 is discussed in the chapter below.

## Pituitary Tumors

Tumors of the pituitary gland rarely complicate genetic conditions other than MEN 1 (see section below). The most common pituitary tumor in MEN 1 is prolactinoma (Burgess et al. 1996), but there are several reports in the literature of familial pituitary adenomas without clinical evidence of MEN 1. Mostly, these are examples of familial acromegaly (Bergman et al. 2000; Gadelha et al. 2000; Tamura et al. 2002) and rarely of prolactinoma (Berezin and Karasik 1995). For over a decade, molecular genetic investigations have been used to argue for and against the hypothesis that familial acromegaly is allelic with *MEN1* (Bergman et al. 2000; Gadelha et al. 2000; Tamura et al. 2002). Recently, germline mutations in *AIP* were described as a predisposition gene for subsets of apparently sporadic and familial acromegaly (Vierimaa et al. 2006). The highest prevalence of germline *AIP* mutations were found in young patients with pituitary macroadenomas (Tichomirowa et al. 2011). Indeed, 20 % of the pediatric cases were found to have such mutations. Pituitary adenomas may occur in CNC and chromophobe adenomas may possibly have an increased frequency in Maffucci syndrome (see section below). No occult germline *PRKARIA* mutations were found in a recent series of 74 pediatric presentations of pituitary adenomas/Cushing disease (Stratakis et al. 2010).

Both somatic tumor suppressor gene inactivation and oncogene activation have been implicated in the pathogenesis of pituitary tumors. Chromosome 11 allele loss (the *MEN1* gene maps to chromosome 11q13) is the most frequent event in sporadic pituitary adenomas, and chromosome 13 allele loss is also frequent. Accordingly, there exist somatic *MEN1* mutations in sporadic pituitary adenomas (Zhuang et al. 1997). Some growth-hormone-secreting pituitary tumors have been found to contain somatic mutations which inhibit the GTPase activity of a G-protein alpha chain and

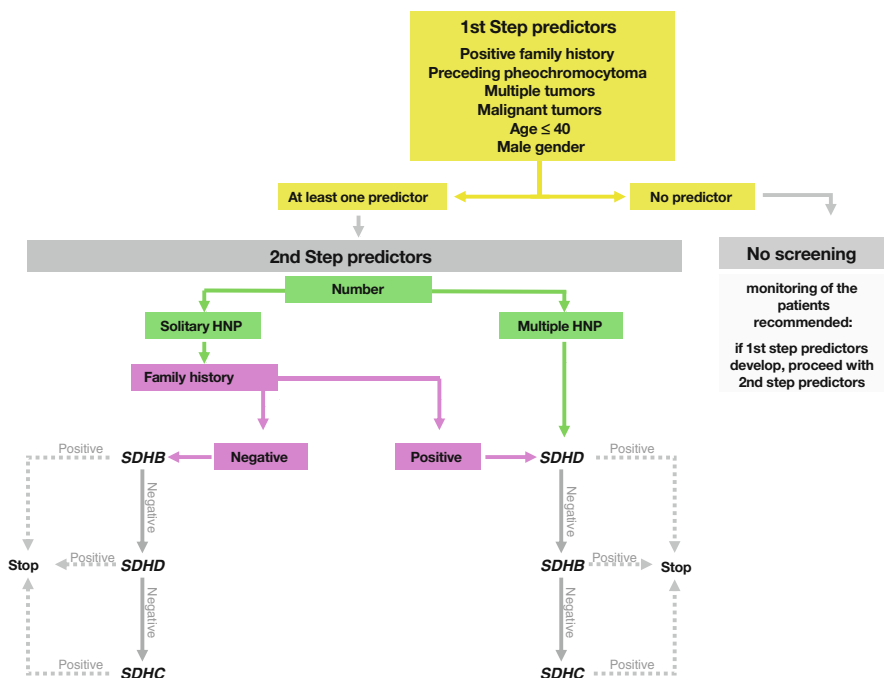
convert it to a putative oncogene *gsp* (Lyons et al. 1990). This results in activation of adenylyl cyclase and bypasses the need for trophic-hormone-mediated activation. Similar mutations have been found in McCune–Albright syndrome (see below).

## Adrenal Gland Tumors

Tumors of the adrenal glands arise from either the medulla or the cortex. Adrenal medullary tumors include neuroblastomas (p. 7), embryonal tumors, and pheochromocytomas.

### *Pheochromocytoma*

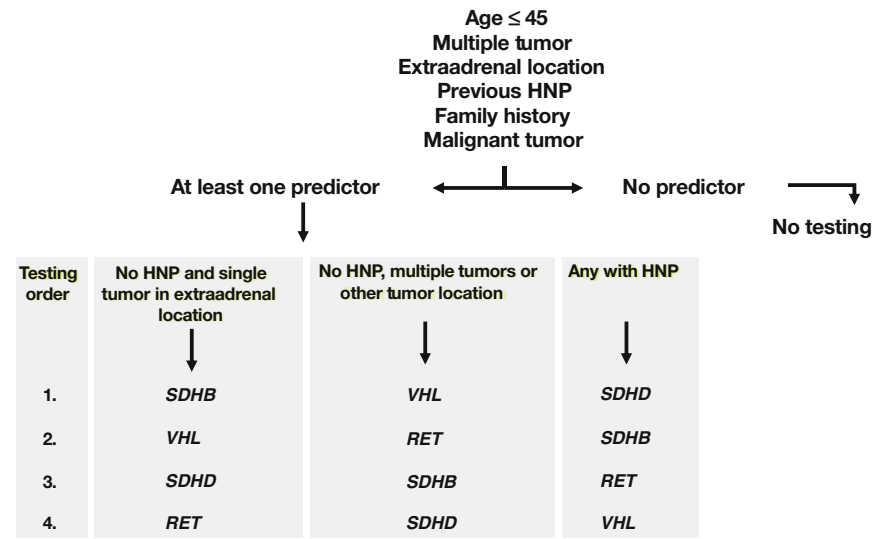
Pheochromocytomas are derivatives of the neural crest and arise from adrenal chromaffin cells. Extra-adrenal (chromaffin) paragangliomas may be referred to as extra-adrenal pheochromocytomas. Medical textbooks have traditionally suggested that approximately 10 % of pheochromocytomas are heritable, 10 % are extra-adrenal, and 10 % are malignant. However, the frequency of heritable pheochromocytoma has been underestimated, and in one population-based study, 25 % of unrelated, apparently sporadic presentations of pheochromocytomas, without syndromic features or family history, were found to harbor germline mutations in one of four genes, *VHL*, *RET*, *SDHD*, or *SDHB* (Neumann et al. 2002). This frequency has been confirmed in referral series as well (Benn et al. 2006). Due to these and related findings, all presentations of pheochromocytomas, regardless of age, syndromic features, or family history, should be considered for mutation analysis in the setting of cancer genetic consultation which includes genetic counseling. The genetic differential diagnosis of pheochromocytoma includes MEN 2 caused by germline mutations in the *RET* gene; von Hippel–Lindau (*VHL*) disease caused by *VHL* mutations; the pheochromocytoma–paraganglioma syndrome caused by germline mutations in the *SDHB*, *SDHC*, and *SDHD* genes; and, very rarely, NF 1 (Maher and Eng 2002; Eng et al. 2003; Neumann et al. 2004; Schiavi et al. 2005) (see below and section to follow). Familial site-specific pheochromocytomas are mainly attributable to germline mutations in *VHL*, *SDHD*, or *SDHB* (Woodward et al. 1997; Astuti et al. 2001a, b). Such families with pheochromocytomas as well as chemodectomas or glomus tumors are almost always due to germline mutations in *SDHB*, *SDHC*, or *SDHD* (Maher and Eng 2002; Neumann et al. 2004). Recently, germline mutations in *TMEM127* were described in rare familial adrenal pheochromocytoma cases (Yao et al. 2010). These cases were characterized by unilateral tumors diagnosed in the 40s. However, a subsequent registry-based study demonstrated that germline *TMEM127* mutations could also be associated with extra-adrenal disease, occurring in about 5 % of 48 individuals with paraganglioma but without mutations in the other predisposition genes (Neumann et al. 2011). Even more recently, germline *MAX* mutations were described in ~10 % of hereditary pheochromocytoma cases characterized by very early-onset and malignant disease (Comino-Mendez et al. 2011).



**Fig. 4.1** Genetic testing algorithm for pheochromocytoma presentations (Reproduced from AACR Journal paper, which is authored/coauthored by at least one of the authors of this book)

In general, like virtually all inherited neoplasias, the mean age at diagnosis for heritable pheochromocytoma is lower, and there will be a higher incidence of bilateral tumors and multifocal disease when compared to sporadic pheochromocytoma. Nonetheless, these clinical features, the clinical hallmarks of heredity, are syndrome dependent (and hence, dependent on susceptibility gene involved) (Neumann et al. 2004). For example, in the population-based study on non-syndromic pheochromocytomas, while the mean age at presentation in individuals without germline mutations (sporadic) was 44 years, the mean age was 36 years for those shown to carry a *RET* mutation (MEN 2), 18.3 years for *VHL*, and approximately 27 years for those found to have germline *SDHD/SDHB* mutations (Neumann et al. 2002). NF 1-related pheochromocytomas are usually diagnosed relatively older, around 40 years. Further, of those found to carry germline mutations, about one-third presented with multifocal disease compared to two-thirds with a solitary lesion (Neumann et al. 2002). Therefore, two algorithms were computed to help clinicians determine whether to offer germline gene testing in pheochromocytoma and paraganglioma presentations, and if so, then which genes to prioritize [Fig. 4.1 of Erlic and Fig. 4.2 of Neumann] (Erlic et al. 2009; Neumann et al. 2009).





**Fig. 4.2** Clinical algorithm to priorities whether genetic testing is warranted (first step predictors), and if so which gene(s) to prioritize (second step predictors) for pheochromocytoma presentations (Reproduced from AACR Journal paper, which is authored/coauthored by at least one of the authors of this book)

There has been scant information regarding somatic mutations in sporadic pheochromocytoma except for relatively low frequencies of somatic *VHL* mutations, somatic *RET* mutations, and somatic *SDHD* mutations (Eng et al. 1995a, b; Gimm et al. 2000; Astuti et al. 2001a, b). Interestingly, differential distributions of frequencies of LOH at 1p, 3p, and 22q exist between *VHL*-related pheochromocytomas and those of sporadic tumors (Bender et al. 2000). In *VHL*-related pheochromocytomas, almost all showed LOH of markers around *VHL* at 3p with LOH of markers at 1p and 22q being 15 and 21 %, respectively. In contrast, sporadic tumors showed LOH at 3p in only 21 % of samples but relatively high frequencies of 1p and 22q marker LOH (Bender et al. 2000). In MEN 2-related pheochromocytoma, it is believed that amplification of the mutant *Ret* allele could contribute to carcinogenesis in an unknown proportion of tumors (Huang et al. 2000). Despite genome-wide approaches, mainly of the transcriptome, clarity in regard to somatic alterations did not go beyond what was already known for 10 years. Recently, integrative genomic approaches utilizing 202 sporadic and 75 hereditary pheochromocytoma and paraganglioma tumors revealed that ~45 % carried some form of germline or somatic alteration, with 14 % harboring *VHL* or *RET* mutations (Burnichon et al. 2011). As found previously, transcriptome signatures were consistent with germline status and clearly distinguished *VHL*-related from *SDHx*-related tumors (Burnichon et al. 2011).

Individuals at risk for pheochromocytoma should be offered annual surveillance. The precise measures for clinical surveillance are dependent on the specific syndrome at risk for and the institution. In general, annual physical examination paying particular attention to the retinal examination and blood pressure measurements,

**Table 4.2** Sample surveillance protocol for SDH mutation carrier

Proven <i>SDHB</i> mutation carrier
Annual 24-h urine for catecholamines and vanillylmandelic acid measurements from age 5 years
Annual abdominal MRI scans from age 7 years (abdominal and thoracic every 3 years)
MRI neck age 20 years and every 3 years thereafter
Proven <i>SDHD</i> mutation carrier (paternally transmitted)
Annual 24-h urine for catecholamines and vanillylmandelic acid measurements from age 5 years
Two yearly abdominal MRI scans from age 7 years (abdominal and thoracic every 5 years)
MRI neck age 20 years and every 1–2 years thereafter

especially with orthostatic maneuvers, and 24-h urinary catecholamines and vanillylmandelic acid measurements are performed. Some centers advocate serum catecholamine, vanillylmandelic acid, and chromogranin-A measurements as well. Further investigation may include MIBG and computerized tomography (CT) or magnetic resonance imaging (MRI) scans and selective venous sampling as appropriate. Recently, positron emission tomography (PET) scanning is performed for surveillance in certain centers. Full details of screening protocols in VHL disease, NF1, and MEN 2 are described in the Chap. 11, and a sample screening protocol for *SDHB* and *SDHD* gene carriers is suggested in Table 4.2.

## Adrenocortical Adenoma and Carcinoma

Adrenocortical tumors are rare (incidence approximately 0.2 per 100,000 per year) and may be benign or malignant. The most frequent presentation is with Cushing syndrome with or without associated virilization, sometimes with primary aldosteronism; estrogen-producing tumors are rare. Adrenocortical carcinomas are proven component cancers in Li–Fraumeni syndrome caused by germline *TP53* mutations (see below for complete discussion of this syndrome). Indeed, early-onset (under the age of 4 years) or bilateral disease carries a high likelihood of germline *TP53* mutation (Malkin et al. 1990; Eng et al. 1997). In a series of 14 patients with adrenocortical carcinoma unselected for family history, 11 (82 %) carried a germline *TP53* mutation. Interestingly, the same two mutations (at codons 152 and 158) were present in 9 of the 11 mutation-positive cases. In another series of 36 cases of childhood adrenocortical carcinoma in southern Brazil, 35 carried an identical R337H mutation (Ribeiro et al. 2001). Some believe that adrenocortical carcinomas can be found at increased frequencies in Beckwith–Wiedemann syndrome (Wiedemann 1983).

A macroscopically and histologically distinctive type of adrenocortical hyperplasia called primary pigmented nodular adrenocortical disease (PPNAD) is a component neoplasia of CNC (NAME syndrome) and is discussed below. PPNAD can be clinically diagnosed by its paradoxical response to dexamethasone challenge (Stratakis et al. 1999). Benign adrenocortical lesions, usually nonfunctional, are reported in MEN 1 patients, some believe as frequently as 20–40 %. Adrenocortical nodular hyperplasia and rarely adenoma may be seen in McCune–Albright syndrome

(see below). Hypercortisolism is often associated with macronodular hyperplasia of the adrenal cortex. Recently, germline variation in *PDE11* has been associated with macronodular hyperplasia of the adrenal cortex (Horvath et al. 2006).

## Glomus Tumors (Non-chromaffin Paraganglioma)

Glomus tumors are benign tumors of the head and neck region derived from neural crest and are situated predominantly at the carotid bifurcation and jugular foramen. Glomus tumors, sometimes referred to as chemodectomas, are the most common type of paraganglioma in the head and neck region. They are non-chromaffin paragangliomas, that is, they do not secrete but instead are sensing organs. Glomus tumors have an incidence of approximately 1 in 30,000 and are usually sporadic and unilateral. However, about a third of multiple cases are familial, with an autosomal dominant inheritance pattern. Bilateral disease is significantly more frequent in familial (32–38 % of cases) than in nonfamilial (4–8 %) cases (Grufferman et al. 1980; Parry et al. 1982). Six percent of patients with familial chemodectomas develop second primary tumors, predominantly other paragangliomas. The inheritance of some instances of familial glomus tumors shows maternal imprinting: descendants of affected females who inherit the gene do not develop glomus tumors, but heterozygote descendants of affected males do. Two loci for familial glomus tumors in Dutch kindred have been mapped to the long arm of chromosome 11: PGL1 at 11q23.1 and PGL2 at 11q13 (Heutink et al. 1992; Mariman et al. 1995). Germline mutations in *SDHD* on 11q23.1 (PGL1) were described in families with glomus tumors with and without thoracic/adrenal paragangliomas (Baysal et al. 2000). In mutation-positive families, maternal imprinting was demonstrated. Perhaps because of maternal imprinting, occult germline *SDHD* mutations are evident in a relatively high frequency of apparently sporadic adrenal pheochromocytoma or paraganglioma patients (Gimm et al. 2000). Subsequently, germline mutations in *SDHB* (PGL4) in individuals and families with paraganglioma and/or pheochromocytomas were described (Astuti et al. 2001a, b). Interestingly, only two families with paragangliomas have been described with germline *SDHC* (PGL3) mutations (Niemann and Muller 2000). The gene on 11q13 underlying PGL2 eluded identification for many years, and only a single Dutch family is linked to this locus. Recently, *SDHAF2* (*hSdh5*) was identified as PGL2 (Hao et al. 2009). This gene rarely accounts for paraganglioma, and not surprisingly a single founder mutation Gly78Arg is the most common (Bayley et al. 2010). Initially thought only to predispose to pheochromocytoma, germline *TMEM127* has also been shown to predispose to paraganglioma (Yao et al. 2010; Neumann et al. 2011). Even more recently, germline *MAX* mutations were described in ~10 % of hereditary pheochromocytoma cases characterized by very early-onset and malignant disease (Comino-Mendez et al. 2011). Paragangliomas may occur in CNC (p. 228 – ex-176) or MEN 1 (p. 277).

In a population-based registry of head and neck paragangliomas, accrued without regard to clinical features, demographics, or family history, over 2/3 were due to

germline *SDHD* mutations, 1/3 *SDHB* mutation, and, rarely, *SDHC* (Neumann et al. 2004; Schiavi et al. 2005; Peczkowska et al. 2007; Peczkowska et al. 2008). Unless there are other clinical features of or family histories, head and neck paragangliomas are rarely, if ever, associated with MEN 2 or VHL (Boedeker et al. 2009). Because there are multiple genes associated with head and neck paragangliomas, a clinically relevant algorithm was modeled which takes into account demographic, clinical, and gene-specific prevalence data to help prioritize which presentations should be offered genetic testing, and if so, which gene to prioritize. Using such an algorithm, a cost reduction of >50 % was achieved (Neumann et al. 2009).

## Pancreatic Endocrine Tumors

Non-endocrine pancreatic tumors are described on page 52. Pancreatic endocrine tumors (islet cell adenomas such as gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma) may occur in up to 1.5 % of autopsies but are mostly asymptomatic. Pancreatic endocrine tumors are a feature of MEN 1 and VHL disease (see Chap. 11).

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## Chapter 5

# Gastrointestinal System

### Salivary Gland Tumors

Tumors at this site occur with a frequency of about 1 per 100,000 population. They are commoner in Spanish, Inuit, Indian, and Cantonese Chinese populations, but do not appear to have a strong genetic basis. Familial occurrence of mixed salivary tumors has been reported infrequently (Klausner and Handler 1994), and it is difficult to know whether the familial incidence is determined by hereditary or environmental factors. However, similarities in the epidemiology of nasopharyngeal carcinoma and salivary gland tumors suggest that they may have a similar etiology, perhaps involving Epstein–Barr virus (EBV) infection (Ponz de Leon 1994). Several Greenland Inuit families have been described with two or more siblings affected, and there was an increased risk of other cancers in these sibships (Merrick et al. 1986). Other studies from Greenland show that a significant fraction of all cases occurring among Greenland Inuit clusters in families (Albeck et al. 1993). Cancer incidence in this part of the world differs from that seen in more temperate climates: compared to the Caucasian population in Denmark (1973–1995), high standardized incidence ratios (SIRs) were found for cancers of the salivary gland and nasopharynx (EBV-related cancers), esophagus, stomach (probably related to a dried fish diet), and cervix (HPV-related). Low SIRs were seen for testis, bladder, prostate, breast, and hematological cancers (Friborg et al. 2003). In a further study in the same population, there was about an eightfold increased risk of salivary gland carcinoma in first-degree relatives of patients with nasopharyngeal carcinoma (none of the salivary gland carcinoma patients developed subsequent nasopharyngeal carcinoma in the follow-up period) (Friborg et al. 2005).

A single two-generation Inuit family from northern Quebec (Nunavik) that contained four family members of both sexes, all diagnosed with lymphoepithelioma of the parotid gland (without involvement of the nasopharynx), has been reported (Vu et al. 2008). Rare families with familial neuroendocrine carcinoma of the salivary glands and deafness and enamel hyperplasia (siblings) are described (Michaels et al. 1999).

MALT lymphomas may occur in the lymphoid tissue of the salivary glands, often associated with a translocation t (14:18 [q.32;q.21]) (Streubel et al. 2003). MALT lymphomas may develop in benign lesions developing from long-standing Sjogren's syndrome. There has been a case report of a 3-year-old child with a plexiform neurofibroma involving the submandibular salivary gland that mimicked an intraglandular tumor (Bourgeois et al. 2001). There was a family history of neurofibromatosis.

Germline mutations in the *CYLD1* gene may cause Brooke–Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma 1 (see p. 200). Salivary gland tumors (adenomas and adenocarcinomas) may be a feature of these disorders (Kakagia et al. 2004; Bowen et al. 2005).

## Gastrointestinal System

Tumors of the gastrointestinal system are among the most common tumors in humans, and although environmental influences have been clearly implicated, heredity is recognized as being of major importance in their etiology.

### Esophageal Tumors

The incidence of squamous cell carcinoma of the esophagus shows marked geographical variation, with a high frequency in the Caspian littoral of Iran, certain parts of the interior of China, and the Transkei region of South Africa. There is a low incidence in European and North American Caucasian populations. Oropharyngeal tumors are also commoner in areas with a high incidence of esophageal cancer. These findings are thought to be the result of differences in exposure to ingested carcinogens rather than of major genetic factors, although the at-risk individuals who develop this cancer in these high-risk areas are predominantly of Mongol or Turkic origin. The incidence of esophageal cancer in the UK is 6 per 100,000, and it is commoner in males. Almost all (98 %) of esophageal cancers are squamous carcinomas.

Early studies suggested that genetic factors do not play a major role in most cases of esophageal cancer as there did not appear to be an increased risk to relatives of index cases (Mosbech and Videbaek 1955), and recent studies in the United States have been in agreement (Dhillon et al. 2001). However other studies, particularly those in high-incidence regions, such as China, have come to the conclusion that the familial occurrence of esophageal cancer probably does have a Mendelian basis, with both autosomal dominant (Zhang et al. 2000; Guohong et al. 2010) and recessive models favored. A genome-wide search indicated that chromosome 13 could harbor such a gene, but sequence analysis of known candidate genes, such as *BRCA2*, has been inconclusive (Hu et al. 2002, 2004) (see below, however). Interestingly, gene expression studies indicate that true differences exist between familial and nonfamilial esophageal cancer, suggesting that there are susceptibility genes to be found (Su et al. 2003).

The autosomal dominant condition of late-onset tylosis (keratosis palmaris et plantaris), with hyperkeratosis of the palms and soles from late childhood to adolescence, is associated with a high incidence of esophageal cancer (p. 200; Shine and Alison 1966; Risk et al. 2002). Tylosis with onset in infancy does not seem to be associated with any such increased cancer risk. Thickening of the skin of the pressure areas on the soles of the feet is seen, and oral leukokeratosis and follicular hyperkeratosis occur. The risk of esophageal cancer reaches 95 % by 63 years of age, and the mean age at diagnosis of the cancer is 45 years of age. Prophylactic esophagectomy with interposition of a segment of colon has been suggested for affected individuals. If prophylactic esophagectomy has not been performed, then annual esophagoscopy is recommended, and immediate esophagectomy is advisable if dysplasia is detected. The gene for this condition was mapped to chromosome 17q, and a presumed gain-of-function mutation in *RHBDF2* has been reported as the cause (Hennies et al. 1995; Kelsell et al. 1996; Langan et al. 2004; Blaydon et al. 2012; Saarinen et al. 2012).

There is an increased risk of esophageal cancer in Fanconi anemia (Alter 1996; Rosenberg et al. 2003; see p. 249) and possibly also in epidermolysis bullosa (p. 195), dyskeratosis congenita (p. 194), and congenital abnormalities of the esophagus, such as strictures. In support of the earlier epidemiological data, mutations in genes in the Fanconi anemia pathway have been associated with esophageal cancer in Iran – most notably, *BRCA2* (*FANCD1*), where the p. Lys3326X mutation was present in 27 of 746 esophageal squamous cell cancer cases and in 16 of 1,373 controls (OR=3.38, 95 % CI=1.97–6.91,  $P=0.0002$ ) (Akbari et al. 2011). This is a notable finding because this particular *BRCA2* mutation is generally not thought to be a cause of breast cancer susceptibility.

The risk of esophageal cancer increases with celiac disease (p. 231) and is more common in the adult-onset form, but is probably uncommon when celiac disease is diagnosed and treated in childhood or infancy. There is an increased risk of esophageal cancer in achalasia. This condition is not usually genetic, but its familial occurrence has been described occasionally with some evidence of an autosomal recessive subgroup (Frieling et al. 1988; Gockel et al. 2010). Nevertheless it may occur rarely as part of a genetic condition (autosomal recessive), characterized by achalasia, alacrimia, and sensorimotor polyneuropathy (Achalasia–Addisonianism–Alacrimia syndrome, also known as Allgrove syndrome), and the responsible gene, *AAAS*, has been identified (Kasirga et al. 1996; Handschug et al. 2001).

There is also an increased risk of adenocarcinoma of the esophagus (possibly 10 %) in Barrett esophagus, in which columnar rather than squamous epithelium is found with chronic ulcerative esophagitis. Although this is usually sporadic, some familial cases have been described, and 70 families have recently been reported (Drovdlic et al. 2003). Importantly, there was no excess of extra-esophageal cancers in these families. In unselected individuals with Barrett esophagus, it is among older males that most familial cases are encountered (Chak et al. 2002). Germline mutations in *MSR1* have been reported in a small proportion of patients with Barrett esophagus/esophageal cancer (Orloff et al. 2011).

## Management

In tylosis, annual esophagoscopy is recommended unless prophylactic esophagectomy has been performed, and because of the high risk of cancer in this disorder, immediate esophagectomy is advisable if dysplasia is detected. However, in other conditions in which the risk of carcinoma is less, the appropriate course of action if an abnormality is found may not be so clear, and results from an observational study of individuals undergoing surveillance for Barrett esophagus found that there was no impact on overall mortality (MacDonald et al. 2000). Nevertheless, those with a family history are likely to be screened by endoscopy even if they do not have long-segment disease. Screening for esophageal cancer by endoscopy with multiple biopsies to detect dysplasia is performed in some high-risk areas in China (Spigelman and Phillips 1991).

## Gastric Tumors

Benign tumors of the stomach are uncommon. Polyploid adenomas occur in less than 1 % of the population and may occur in association with intestinal metaplasia. They predispose to carcinoma. Gastric polyps occur in familial adenomatous polyposis (in up to two-thirds of patients, but with a lower potential for malignant transformation than the colonic adenomas; see p. 241), in MUTYH-associated polyposis, in Peutz–Jeghers syndrome (p. 299), and in Cowden syndrome (p. 233). Gastric polyposis (with malignant potential) limited to the stomach has been described in three generations of a family (dos Santos and de Magalhes 1980). Recently three families with an autosomal dominantly inherited syndrome characterized by fundic gland polyposis and intestinal-type gastric cancer was described (gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)) (Worthley et al. 2012). Recommended diagnostic criteria for GAPPS were (1) gastric polyps restricted to the body and fundus without colorectal or duodenal polyposis, (2) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree relative of another case, (3) predominantly fundic gland polyps with regions of dysplasia or gastric adenocarcinoma, and (4) autosomal dominant inheritance. Earliest age at diagnosis of gastric cancer was 33 years of age. Relatives at high risk should be offered surveillance gastroscopy, and partial gastrectomy should be considered in affected cases.

Hyperplastic gastric polyps are five times as common as gastric polyps and have a much lower risk of malignancy. They are found with increased frequency in pernicious anemia and in familial adenomatous polyposis (Debinski et al. 1995) and the Peutz–Jeghers syndrome (Ushio et al. 1976; Williams et al. 1982). Carcinoids, lymphomas, sarcomas, and leiomyosarcomas may also arise in the stomach; a family with primary B cell gastric lymphoma in a father and his two daughters has been described (Hayoz et al. 1993).

## Gastric Carcinoma

The incidence of gastric cancer (which is adenocarcinoma in 97 % of cases) shows marked geographical variation, being 88 per 100,000 males in Japan and 22 and 11 per 100,000 in the UK and USA, respectively. Women have about half the male incidence. There is a twofold to threefold excess risk of gastric cancer in the first-degree relatives of affected patients, particularly in cases diagnosed under the age of 50 years of age. Two major histological variants of gastric cancer are recognized: a diffuse type containing signet ring cells and intestinal-type gastric cancer which is associated with the presence of *H. pylori*. The latter is preceded by chronic gastritis, atrophy, and metaplasia. However, the diffuse histological type does not have recognized precursor changes (Correa and Shiao 1994). An association between blood group A and gastric cancer (particularly the diffuse type) has long been recognized. This could in part be due to the association of this blood group with pernicious anemia, which itself carries a higher than expected risk of gastric cancer (McConnell 1966). The risk of gastric cancer in relatives of index cases appears to be much more pronounced when the histological type in the index case is diffuse (seven times the risk in matched controls) rather than of the intestinal type (1.5 times higher than in control families) (Macklin 1960), but only a small proportion of diffuse gastric cancers occurs in families with an autosomal dominant gastric cancer susceptibility (reviewed in González et al. 2002).

The diffuse type of gastric carcinoma demonstrates a nearly equal sex ratio (compared with a male preponderance in the intestinal type), a younger patient age distribution, and little change with geographical migration, relative to the intestinal type. Chronic atrophic gastritis is found with increased frequency in relatives of index cases with pernicious anemia and gastric adenocarcinomas, but, specifically, it has been demonstrated to be more frequent in the relatives of index cases with diffuse spreading carcinoma than in controls; this has not been seen with other gastric cancer types (Kekki et al. 1987). Evidence suggests there may be an association between chronic *H. pylori* infection and intestinal-type chronic gastritis and cancer susceptibility: an increased frequency of infection with this organism has been reported in stomach cancer patients (Scott et al. 1990). Chronic gastritis may have a hereditary component, but the nature of this and its relationship to *Helicobacter* infection have not been clearly elucidated (Kekki et al. 1987). Ménétrier's disease is also associated with an increased risk (10 %) of gastric cancer – possibly because atrophic gastritis occurs in this etiologically obscure disease.

Most gastric cancers are sporadic, although up to 3 % occur in predisposed individuals. Nevertheless, there are many reports of families in which there is a strikingly high incidence of gastric cancer, following an autosomal dominant pattern of inheritance (Triantafyllidis et al. 1993; Villanueva et al. 2010). Napoleon Bonaparte came from such a family (Creagan and Fraumeni 1973). Gastric cancer is a component of Lynch syndrome (see below). An increased incidence of stomach cancer has also been noted in the close relatives of women with the medullary or tubular histological types of breast cancer. Some of these families may have Li–Fraumeni syndrome (Burki et al. 1987), and gastric carcinoma has also

been described in some families with p53 mutations (Varley et al. 1995). Lobular breast cancer is increased in families with germline *CDH1* mutations (see below).

Adenocarcinoma of the stomach is reported in familial adenomatous polyposis (Jagelman et al. 1988) and is also reported to be more frequent in ataxia telangiectasia (Haerer et al. 1969; see p. 219 Gylling et al. 2007; Ohue et al. 1996) and in patients with immune deficiency. IgA deficiency is associated with an increased risk of intestinal metaplasia and of gastric cancer. The inheritance of IgA deficiency is not clear-cut and may be multifactorial (Grundbacher 1972). Gastric cancer occurs with increased relative risk in carriers of germline *BRCA2* mutations (Breast Cancer Linkage Consortium 1997; Jakubowska et al. 2002). Gastric carcinoma (particularly of the intestinal type) is also part of the spectrum of cancers found in Lynch syndrome and displays replication errors (RER) characteristic of the condition in such families. The average age at diagnosis of gastric carcinoma in Lynch syndrome has been reported to be 56 years of age (Arnio et al. 1997; Watson et al. 2008).

The International Gastric Cancer Linkage Consortium (IGCLC) defined hereditary diffuse gastric cancer (HDGC) as (a) families with two or more cases of diffuse gastric cancer in first- or second-degree relatives with one affected aged <50 years or (b) three cases or more cases of diffuse gastric cancer in first- or second-degree relatives at any age (Caldas et al. 1999; Pharoah et al. 2001). Overall, about 25–50 % of patients with HDGC will have germline *CDH1* mutations, and this rises to about 50 % in younger-onset cases (<50 years) with a positive family history (Gayther et al. 1998; Guilford et al. 1998; Richards et al. 1999). However isolated early-onset cases of diffuse gastric cancer are unlikely to have germline *CDH1* mutations (Brooks-Wilson et al. 2004). Recently, it was suggested that families meeting the HDGC criteria should be offered testing for *CDH1* mutations, and in addition, *CDH1* molecular genetic testing also should be considered in (a) families with two cases of gastric cancer in the family with one confirmed case of diffuse gastric cancer <50 years, (b) cases of diffuse gastric cancer aged <40 years, and (c) a personal or family history of diffuse gastric cancer and lobular breast cancer (with one diagnosed <50 years of age). About 4 % of *CDH1* mutation-positive families have exonic deletions.

The lifetime risk of gastric cancer in *CDH1* mutation carriers was originally estimated to be >80 %, and prophylactic gastrectomy should be offered to mutation carriers aged 20 years or older (Fitzgerald et al. 2010), and multiple foci of gastric cancer have been found in gastrectomy specimens from affected individuals (Huntsman et al. 2001). If gastrectomy is delayed, then intensive annual endoscopy with multiple biopsies should be performed, but the efficacy of such screening is uncertain, as multiple foci of gastric cancer have been detected in gastrectomy specimens from affected individuals previously screened in this way (Huntsman et al. 2001). Chromoendoscopic surveillance has also been advocated (Shaw et al. 2005), but is generally thought to be too insensitive to replace preventive surgery.

Further large-scale studies of penetrance are required as the long-term effects of total gastrectomy remain uncertain.

There is an increased risk of breast cancer, particularly lobular, in women with germline *CDH1* mutations, and it has been recommended that such women should have annual mammogram and breast MRI and biannual clinical breast examination



from 25 years of age (Fitzgerald et al. 2010). In *CDH1* mutation-positive families with a history of colorectal cancer, mutation carriers might be offered colonoscopy from 40 years of age or, if younger, 10 years younger than the earliest age of onset of colorectal cancer in the family (Fitzgerald et al. 2010).

For individuals at risk for familial gastric cancer without *CDH1* mutations, endoscopy with eradication of *H. pylori* infection is performed as an initial step. Subsequent endoscopies may be performed annually.

## Hepatic Tumors

Cancer of the liver typically occurs as hepatocellular carcinoma or intrahepatic bile duct cancer (cholangiocarcinoma) in adults and as hepatoblastoma in childhood.

### Hepatoblastoma

This rare embryonal tumor originates from immature liver cells. It usually presents in children under 3 years of age, is more common in males than in females, and shows no association with hepatitis B infection or cirrhosis. The majority of cases of hepatoblastoma are sporadic, although familial cases occasionally occur (Hartley et al. 1990). Congenital abnormalities, particularly abnormalities of the urogenital system, are more common in children who develop hepatoblastoma. Syndromes associated with an increased susceptibility to hepatoblastoma development include Beckwith–Wiedemann syndrome and congenital hemihypertrophy, caused by dysregulation of the 11p15 growth region. Risk of neoplasia in children with this disorder is increased if hemihypertrophy is present, and children with BWS and loss of methylation at KvDMR1 appear to be at higher risk of hepatoblastoma than Wilms' tumor (Cooper et al. 2005). It is not a component of another overgrowth syndrome, Bannayan–Riley–Ruvalcaba syndrome. Hepatoblastoma may occur in children with familial adenomatous polyposis (Herzog et al. 2000) (p. 241). Hepatoblastoma surveillance for individuals at increased risk is controversial. Some clinicians advocate 3 monthly physical examinations, serum  $\alpha$ -fetoprotein, and abdominal ultrasound until the age of 3 years and then 6 monthly until 6 years of age (Chitayat et al. 1990a, b; Clericuzio et al. 2003). However, there is little evidence for the efficacy of this screening program, and currently the potential benefits and risks are poorly understood.

### Hepatocellular Carcinoma

Most cases of hepatocellular carcinoma occur in adults, appear to be sporadic, and are related to environmental carcinogens such as hepatitis B viral infections and aflatoxin. The marked geographical variations in the incidence of hepatocellular



**Table 5.1** Genetic causes of liver cancer

Important causes	Less commonly associated
Hemochromatosis	Galactosemia
$\alpha_1$ -Antitrypsin deficiency	Hereditary fructose intolerance
Glycogen storage disease	Iron overload in thalassemia
Type I (hepatic)	Iron overload in hereditary hemorrhagic telangiectasia
Type IV	Acute intermittent porphyria
Tyrosinemia	Common bile duct atresia
Fanconi anemia	Neonatal hepatitis
Wilson disease	Cystic fibrosis
	De Toni–Fanconi syndrome
	Werner syndrome
	Familial cirrhosis
	Indian childhood cirrhosis
	Neonatal giant cell hepatitis
	Neonatal hemochromatosis
	Porphyria cutanea tarda

carcinoma (it is frequent in Africa and Asia, reaching an incidence of 40 per 100,000 males) are thought to be caused by environmental factors. The incidence in the UK is 1–1.6 per 100,000, and it is commoner in males. Familial clustering of hepatocellular cancer has occasionally been reported (Fernandez et al. 1994; Drinkwater and Lee 1995), and the relative risk of the cancer in the first-degree relatives of index cases with primary liver cancer has been assessed to be 2.4 (Fernandez et al. 1994). However, familial clustering of hepatitis B virus is common as a consequence of perinatal transmission, and this is regarded as the main cause of familial hepatocellular carcinoma in high-prevalence areas (Tai et al. 2002).

Liver cancer may occur as a complication of chronic liver disease and cirrhosis of a variety of causes (although it is rare in biliary cirrhosis), some of which have a genetic basis (see Table 5.1). In hemochromatosis, the incidence of hepatic carcinoma is usually only increased if cirrhosis has developed. Hemochromatosis is a common condition affecting about 1 in 300 individuals of Northern European descent. However, many cases are asymptomatic and women are less severely affected than men because of menstrual blood loss (Brind and Bassendine 1990). Hepatocellular carcinoma develops in up to one-third of cirrhotic cases, in whom the relative risk of hepatoma may be 200 (Edwards et al. 1982). Treatment by phlebotomy before cirrhosis develops appears to prevent malignancy (Niederau et al. 1985), although occasionally liver cancer has been reported in the absence of cirrhosis. The *HFE* gene is closely linked to the MHC class I gene cluster at 6p21 (Feder et al. 1996). The two common *HFE* mutations, p. C282Y and p. H63D, are readily screened. A diagnosis of hemochromatosis can be made in p. C283Y homozygotes and p. C282Y/H63D compound heterozygotes. Screening of at-risk relatives is important as early diagnosis allows treatment with prophylactic phlebotomy, and the prevention of cirrhosis from developing will reduce the risk of hepatocellular cancer (Harrison and Bacon 2005).

$\alpha$ -1 antitrypsin deficiency, particularly with the ZZ phenotype, predisposes to hepatocellular carcinoma (Eriksson et al. 1986). This is an autosomal recessive condition with a frequency of 1 in 2,000 births.  $\alpha$ -1 antitrypsin is a serum protease inhibitor encoded by a gene on chromosome 14q31–q32. The phenotype (Pi type) is determined by isoelectric focusing of serum, and both parental alleles are expressed. PiMZ heterozygotes may also have an increased risk of hepatocellular cancer, but not those with the null–null phenotype. The commonest phenotype in the UK (PiM) is associated with normal levels of AAT, PiZ is associated with 15 % levels of serum AAT, and null variants are associated with no detectable levels. About 10 % of PiZZ individuals develop neonatal cholestatic jaundice, and 25 % of these develop cirrhosis. PiZ adults have a risk relative to the normal population of 7.4 for cirrhosis and 20 for hepatocellular carcinoma (higher in males) (Brind and Bassendine 1990; Perlmutter 1995).

Individuals with type 1 (hepatic) glycogen storage disease, an autosomal recessive condition due to deficiency of glucose-6-phosphatase, often develop liver adenomas, and hepatoblastomas and hepatocellular carcinomas have been described (Ito et al. 1987). Glycogen storage disease type IV (due to a glycogen debrancher enzyme defect) is also associated with cirrhosis and hepatic cancer.

Hepatoma is a significant cause of death in individuals suffering from the autosomal recessive condition of hereditary tyrosinemia (due to a defect in the fumarylacetoacetase gene on chromosome 15q; Sniderman King et al. 1993–2006; Rootwelt et al. 1996), consequent upon the progressive liver disease with cirrhosis in this condition. About a third of affected children develop liver cancer if they survive to 5 years of age.

Other inherited disorders (e.g., galactosemia, hereditary fructose intolerance) may result in chronic liver damage and so predispose to carcinoma of the liver. Wilson disease, an autosomal recessive copper storage disorder, can cause cirrhosis in the absence of successful therapy with chelating agents. The risk of intra-abdominal malignancy (hepatomas, cholangiocarcinomas, and poorly differentiated adenocarcinomas of unknown primary) is substantial in patients followed for >10 years, and surveillance by abdominal ultrasound may be indicated (Walshe et al. 2003). Iron overload can produce cirrhosis of the liver in thalassemia, and hereditary hemorrhagic telangiectasia may occasionally predispose to liver carcinoma. The hepatic porphyrias can be associated with cirrhosis, and primary liver carcinoma (not always in the presence of cirrhosis) has been described in patients with acute intermittent porphyria. Common bile duct atresia, neonatal hepatitis, cystic fibrosis, and the De Toni–Fanconi syndrome are also associated with a risk of cirrhosis and potentially of liver cancer.

Hepatic carcinoma is described in Fanconi anemia (Alter 1996; Rosenberg et al. 2003) and may sometimes be secondary to androgen therapy for the pancytopenia (p. 249). Werner syndrome may also carry an increased risk for liver cancer (p. 318). Familial cases of cirrhosis without a known predisposing cause have been described, but this group is probably heterogeneous and often environmental in etiology. Indian childhood cirrhosis, with onset between 6 and 18 months of age, has been described with familial occurrence (in about 30 % of cases) in India, Pakistan, Sri Lanka, and Burma, but the clinical course is usually

too rapid for liver cancer to have time to develop. Multifactorial inheritance has been suggested for this condition (Muller et al. 1999). Neonatal giant cell hepatitis is a rare autosomal recessive disorder or group of disorders (including neonatal hemochromatosis) in which primary hepatic cancer has occasionally been described.

There are occasional reports of familial hepatomas in the literature, occurring without cirrhosis, but these are rare. In one family, affected individuals also suffered from maturity onset diabetes mellitus of the young (MODY); Bluteau et al. (2002) demonstrated somatic and germline mutations in *TCF1* at 12q24 in patients with hepatic adenomas. MODY type 3 is caused by heterozygous germline mutations in the *TCF1* that encodes hepatocyte nuclear factor 1 (HNF1). Thus *TCF1* inactivation, with or without MODY3, is important in the pathogenesis of hepatic adenoma. The incidence of second malignancies in individuals with hepatocellular carcinoma has been reported to be high (9 %), and the second primaries were of the types seen in the cancer family syndrome, suggesting the involvement of a similar genetic predisposition in these conditions (Miyanaga et al. 1989). A specific mutation in *TP53* (a GC to TA transversion at codon 249) can be frequently demonstrated in sporadic cases of hepatocellular carcinoma and is probably related to the mutagenic action of aflatoxin B1 and possibly also the hepatitis virus.

## **Cholangiocarcinoma of the Liver**

This liver tumor develops from the epithelial cells of the bile duct and occurs more often in males than females; it is 15 times less common than hepatocellular carcinoma. It occurs in individuals about 10 years older than those with hepatocellular carcinoma, and chronic liver disease is not such an important etiological feature. In patients with ulcerative colitis, the risk of biliary tract tumors is about ten times greater than in the general population and may be related to the duration and severity of the colitis. This association is particularly seen in patients of certain HLA haplotypes (HLA B8). Familial aggregation of biliary tract tumors is rarely reported. Periampullary cancers are seen in familial adenomatous polyposis (FAP) (p. 241), and bile duct cancers may also occur with congenital dilatation of the bile ducts or with congenital absence of the gallbladder and cystic ducts.

## **Hepatic Angiosarcoma**

Hepatic angiosarcoma is a rare tumor (occurring in the 50–70-year age group) that may be associated with environmental exposure to agents such as vinyl chloride monomer, Thorotrast, and inorganic arsenic in up to 25 % of cases.

## Tumors of the Gallbladder

Cancer of the gallbladder is relatively rare, with an incidence of 2 per 100,000. It is more common in females and has a peak incidence in the seventh decade. Most gallbladder cancers (95 %) are adenocarcinomas, and cholelithiasis appears to be the most important predisposing factor. The frequency is very high in North American aboriginals and commoner in the Japanese and in Caucasian than in negroid races. There is an increased relative risk of this cancer in the first-degree relatives of index cases of up to 14 (Fernandez et al. 1994). Familial clustering is very rare, but two families in which several cases of this disorder occurred were described in Hispanic Indians from New Mexico, perhaps reflecting a higher genetic risk for this cancer in this racial group (Devor and Buechley 1979). Developmental abnormalities of the pancreatobiliary ducts, including choledochal cysts, are associated with malignancy in situ, but these are rarely familial.

Biliary tract cancer appears to occur with increased frequency in Lynch syndrome (Aarnio et al. 1995; Watson et al. 2008, see p. 256).

## Pancreatic Cancer

In recent years, the incidence of pancreatic cancer has been increasing in industrialized nations, and it now occurs with a frequency of 8–10 per 100,000 population and is more common in males. Pancreatic cancer accounts for about 5 % of all cancer deaths. Tumors of the endocrine pancreas are described on page 43.

Up to 6 % of individuals with pancreatic carcinoma may have a positive family history of the condition, and there is up to fivefold increased risk of this cancer in the first-degree relatives of index cases (Fernandez et al. 1994; Ghadirian et al. 2002). However, familial clustering is relatively rare, but the tumor may occur as part of the spectrum of malignancies in Lynch syndrome (p. 256), in hereditary cutaneous malignant melanoma families, (p. 180), in families segregating *BRCA1*, and especially *BRCA2* mutations (see below, and p. 91). It also occurs as part of Li–Fraumeni syndrome (p. 271), and occurs with increased frequency in Peutz–Jeghers syndrome (p. 299) and in ataxia telangiectasia (p. 219) (Flanders and Foulkes 1996; Lim et al. 2004; Beggs et al. 2010; Mehenni et al. 2006). The occurrence of pancreatic cancer in kindred with several cases of breast cancer is a significant predictor of a germline mutation in *BRCA2* (Ozcelik et al. 1997; see below). In addition, families have been reported in which several cases of cancer of the pancreas have occurred in a sibship, albeit with late age at onset. Although autosomal recessive inheritance has been suggested (Friedman and Fialkow 1976), there is evidence of autosomal dominant inheritance in most affected families (Ehrental et al. 1987; Bartsch et al. 2012; Lynch et al. 1990; Solomon et al. 2012; Evans et al. 1995), and dominant inheritance with incomplete penetrance would be a unifying explanation. The age at onset, histology, sex distribution, and survival of familial pancreatic cancer appear to be similar to those of nonfamilial cases. Mutations in *CDKN2A* (encoding p16)

on chromosome 9p21 are present in some families with multiple cases of cutaneous malignant melanoma, and in some families, the risk of pancreatic cancer is very high, notably in individuals with the Dutch founder mutation (Goldstein et al. 1995a, b, 2004; Ghiorzo et al. 1999; Lynch et al. 2002; de Vos tot Nederveen Cappel et al. 2003; Bartsch et al. 2002; Vasen et al. 2000). By contrast, familial pancreatic cancer without other familial cases of melanoma is not associated with *CDKN2A* mutations (Lal et al. 2000; Bartsch et al. 2002).

Mutations in the breast cancer susceptibility gene, *BRCA2*, are found in some familial pancreatic cancer kindreds (Murphy et al. 2002; Hahn et al. 2003), although several of the mutations were *BRCA2:6174delT*, and studies that did not include a high proportion of Ashkenazi Jews tended to have lower *BRCA2* mutation frequencies. Nevertheless, there is an excess of pancreatic cancers in breast cancer families carrying *BRCA2* mutations, SIR 5.79 in individuals carrying the mutation, and there is also an increase in risk in carriers of mutations in *BRCA1*, SIR 4.11 (Mocci et al. 2013; Thompson and Easton 2002), although some recent data found a fourfold increased risk of pancreatic cancer in *BRCA2* mutation carriers but not in *BRCA1* mutation carriers (Moran et al. 2012). There also seems to be a small increased risk of pancreatic cancer in mutation-negative families with clustering of breast cancer (BRCA), SIR 1.31 (Mocci et al. 2013).

Like *BRCA2*, *PALB2* is a pancreatic cancer susceptibility gene; although the lifetime risk is not known, it is likely to be at least 5 % in carriers of deleterious *PALB2* mutations (Axilbund and Wiley 2012). Notably, many of the families contain women affected by both breast and pancreatic cancer, and studies of both familial and sporadic pancreatic cancer have shown that these mutations are uncommon (reviewed in Tischkowitz and Xia 2010). Thus, sequencing isolated pancreatic cancer cases to look for *PALB2* mutations is likely to have a very low yield. There is some evidence, however, that such mutations could influence response to certain chemotherapeutic agents (Villarroel et al. 2011).

The gene responsible for ataxia telangiectasia (p. 219), *ATM*, has also been identified as a pancreatic cancer susceptibility gene, although as for *PALB2*, it is responsible for less than 5 % of very strongly familial pancreatic cancer families and only a very small proportion of all cases (Roberts et al. 2012).

The Fanconi anemia genes have been implicated in pancreatic cancer, but the true contribution of these genes is uncertain; *FANCA* mutations do not seem to be important overall (Rogers et al. 2004), although two truncating mutations in *FANCC*, both associated with loss of heterozygosity in the tumors, were seen in a series of 421 pancreatic cancer cases seen at the Mayo Clinic (Couch et al. 2005).

One family has been described with a specific form of hereditary pancreatic carcinoma, where there is clear architectural distortion within the pancreas, and a high incidence of dysplasia. In some cases, preventive pancreatectomy has been carried out, and incipient or early cancers were identified. The gene was linked to the telomeric regions of chromosome 4q (Eberle et al. 2002), and subsequently a missense mutation leading to a conserved proline to serine change at amino acid position 239 in the gene encoding palladin was identified in this single family (Pogue-Geile et al. 2006). This finding has not been universally accepted by other researchers in the field, however (Salaria et al. 2007; Slater et al. 2007; Zogopoulos et al. 2007; Klein et al. 2009).

To date, this has been the only family described with this gene mutation, and an interesting feature is precancerous dysplasia and prominent stromal fibrosis and so, early presentations include diabetes mellitus. Pancreatic cancer is reported to occur in familial adenomatous polyposis (p. 241), although the tumors usually actually arise from the ampulla of Vater.

There is an increased risk of adenocarcinoma of the pancreas in hereditary pancreatitis, a well-described but uncommon autosomal dominant condition associated with attacks from childhood of recurrent pancreatitis in affected family members (Kattwinkel et al. 1973). The condition has been mapped to chromosome 7q, and mutations in the cationic trypsinogen gene *PRSS1* have been detected in affected individuals (Whitcomb et al. 1996). One survey showed that among 112 families in 14 European countries (418 affected individuals), 58 (52 %) families carried a p. R122H mutation, 24 (21 %) had the p. N29I mutation, and 5 (4 %) had the p. A16V mutation. Other mutations were very rare, but 19 % of all families had no identified mutations in *PRSS1* (Howes et al. 2004). Other genetic causes of chronic pancreatitis, such as *CFTR* (Sharer et al. 1998; Pezzilli et al. 2003) or *SPINK1* (Witt et al. 2001) mutations, do not appear to frequent in individuals with pancreatic cancer (Malats et al. 2001; Pezzilli et al. 2003; Teich et al. 2003), but there could be instances where it would be worthwhile to look for specific mutations, such as p. EF508 in *CFTR* and p. N34S in *SPINK1* in individuals with pancreatic cancer in the context of chronic pancreatitis (Flanders and Foulkes 1996).

Pancreatic cancer has been described in a case of Williams syndrome, possibly secondary to hypercalcemia (Jensen et al. 1976). Pancreatoblastoma has been described in the BWS (Koh et al. 1986; see p. 221) and rarely, in familial adenomatous polyposis (Abraham et al. 2001). Overexpression of IGF2 may underlie these cancers in both conditions (Kerr et al. 2002).

Screening for pancreatic cancer is extremely difficult because minor abnormalities detected by screening may be difficult to interpret as there is no clear premalignant lesion, and there are no well-recognized protocols. However, abdominal and endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) have been suggested as possible screening methods, although the latter is probably too invasive except for the most high-risk families, where structural abnormalities may be identified (Brentnall et al. 1999); serum CA 19.9 does not appear to be suitably sensitive, but islet amyloid polypeptide may detect early pancreatic cancer. MRI cholangiopancreatography and endoscopic ultrasound are likely to be the most acceptable choices, and a recent meeting of experts suggests that either or both are indicated for high-risk individuals (Canto et al. 2013). Interestingly, this expert group limited those suitable for screening to first-degree relatives (FDRs) of patients with pancreatic cancer from a familial pancreatic cancer kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and *CDKN2A*, *BRCA2*, and Lynch syndrome mutation carriers with  $\geq 1$  affected FDR (Verna et al. 2010; Giardiello and Trimbath 2006; de Vos tot Nederveen Cappel 2011; Brand et al. 2007; Canto et al. 2011; Harinck et al. 2010).

Somatic *KRAS* mutations are common in pancreatic carcinomas, and their detection in pancreatic juice may also be a helpful diagnostic marker; a combination of such indicators may be developed for use in screening for pancreatic cancer in time (Lynch et al. 1996; Urrita and DiMagno 1996), but as yet no clinically useful tests

of this type have emerged. Next-generation sequencing has identified recurrent mutations in *GNAS* in pancreatic cysts that arise in intraductal papillary mucinous neoplasm (IPMN). These mutations may provide a helpful clue when deciding which pancreatic cysts to excise, as the same mutations were found in the associated invasive lesions (Wu et al. 2011).

## Tumors of the Small Intestine

Benign tumors of the small gut are uncommon, the most frequent being leiomyomas and lipomas. Malignant small intestinal tumors are also rare, accounting for about 1 % of all intestinal neoplasms (incidence of 0.5 per 100,000 population in the UK). In order of decreasing frequency, these are adenocarcinomas, carcinoids, lymphomas, and leiomyosarcomas.

Gastric, duodenal, and jejunal adenomas have been reported in 8 %, 31 %, and 53 % of patients with familial adenomatous polyposis, respectively, and the total probability of adenomas developing in the duodenum in FAP is probably 50–90 % (see p. 241), with about 5 % risk of malignancy, and upper gastroenterological malignancy is the most common cause of death in individuals with familial adenomatous polyposis who have had a colectomy (Groves et al. 2002; Burt et al. 1994; De Pietri et al. 1995; Koornstra et al. 2008; Vasen et al. 2008; Bulow et al. 2004). Age is the most important risk factor; there is no clear association between mutation site and the development of duodenal polyposis. The severity of duodenal polyposis is assessed using the Spigelman classification, which classifies severity in five (0–IV) stages. Points are accumulated for number, size, histology, and severity of dysplasia of polyps. Stage I (1–4 points) indicates mild disease, whereas Stage III–IV (5–12 points) implies severe duodenal polyposis. Approximately 80 % of patients with duodenal polyposis have Stage I–III disease, and 10–20 % have Stage IV disease (Spigelman et al. 1989). The risk of developing cancer appears to be related to the Spigelman stage. In one study, 2 of 27 patients with Stage IV disease at the first endoscopy developed cancer compared with 2 of 339 with Stage 0–III. The overall cumulative risk of duodenal cancer at age 57 was 4.5 % (Bulow et al. 2004) and has been estimated at between 7–36 % in individuals with Stage I–IV disease. The rate of progression from adenoma to carcinoma is slow, although it appears that recurrence of adenomas after initial detection and removal of duodenal adenomas is high.

Adenocarcinoma of the small bowel has been reported in families with Lynch syndrome (p. 256), with a lifetime risk of about 4 % and a high relative risk (100–300) (Vasen et al. 1996), and individuals with Lynch syndrome present with small bowel cancer 10–20 years earlier than in the general population. Small bowel cancers may occur in individuals homozygous for MMR gene mutations (Herkert et al. 2011). A high proportion of small intestinal carcinomas (about 45 %) appear to demonstrate microsatellite instability in individuals with Lynch syndrome (Hibi et al. 1997). The cancers seem to be distributed evenly throughout the small bowel, and there is no



clear genotype–phenotype correlation. Screening of the small bowel is not usually advocated in Lynch syndrome, but it has its advocates (Koornstra et al. 2008), and it is technically much easier to do this now that video capsule endoscopy is available. The rarity of small bowel cancer in Lynch families may, however, make this unfeasible in most centers.

Crohn's disease is associated with an increased risk of small intestinal carcinoma, usually in chronic cases (Fresko et al. 1982). Crohn's disease and ulcerative colitis are multifactorial conditions, but the familial contribution is becoming increasingly appreciated, with sibling relative risks of 30–40 for Crohn's and 10–20 for ulcerative colitis, and with the identification of a susceptibility locus, *NOD2/CARD2*, which is one of several susceptibility gene loci for this multifactorial condition (Mathew and Lewis 2004; Cooney et al. 2009).

Celiac disease in adults is associated with an increased risk of small bowel lymphoma and, less commonly, of carcinoma (Holmes et al. 1980). Small bowel lymphomas may develop as a complication of immune deficiency disorders.

Pancreatoduodenal endocrine tumors may occur in MEN1 and these require aggressive management (Bartsch et al. 2000). Hamartomatous polyps occur in the small intestine in Peutz–Jeghers syndrome (PJS) (p. 299), and there is a significant risk of malignant degeneration in these polyps, resulting in a 2–13 % lifetime risk of colorectal cancer (CRC) in affected individuals (Jenne et al. 1998; van Lier et al. 2011). The relative risk of small bowel cancer in PJS has been estimated as 520 (220 to 1,306), with a lifetime risk of 13 %, mean age at diagnosis 41.7 years of age, and age range of 21–84 years of age (Giardiello et al. 2000).

Other small bowel tumors are rare but may have genetic implications. Carcinoid tumors are rarely syndromic, hamartomatous polyposis of the upper gastrointestinal tract has been reported in Gorlin syndrome (p. 252), small intestinal neurofibroma may complicate NF1 (p. 288), and angiomas of the small gut occur in hereditary hemorrhagic telangiectasia. There have been rare reports of familial polyposis of the entire gastrointestinal tract, but these may be cases of FAP (Yonemoto et al. 1969). Gastrointestinal stromal tumors (GIST), leiomyomas, and leiomyosarcomas may occur, and germline c-kit mutations have been described in individuals with familial GISTs and hyperpigmentation (Robson et al. 2004). Leiomyoma of the small intestine has been described in neurofibromatosis type 1, but is uncommon (Chu et al. 1999).

Upper gastrointestinal surveillance is advocated for individuals with FAP from the age of 25–30 years of age, the frequency depending on the Spigelman score (Vasen et al. 2008). Individuals with Peutz–Jeghers syndrome should be offered a baseline upper GI endoscopy at 8 years followed by 3-yearly video capsule endoscopy (VCE) from 18 years of age (Beggs et al. 2011; van Lier et al. 2011; Cairns et al. 2010). If polyps were detected at 8 years of age, VCE should be performed 3 yearly from that age. Magnetic resonance enterography (MRE) and barium follow-through (BaFT) are reasonable alternatives in adult patients, but BaFT is not favored in children due to radiation exposure. Colonoscopy is also advised every 2–3 years from 40 years of age in individuals with PJS (Giardiello et al. 2005; Giardiello and Trimbath 2006).



**Table 5.2** Conditions associated with gastrointestinal polyposis

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1. <i>Adenomatous polyposis</i>
FAP (and variants such as Gardner and Turcot)
MUTYH-associated polyposis (MAP)
CMMRD <sup>a</sup> (biallelic mismatch repair gene mutations)
<i>POLE</i>
<i>POLD1</i>
2. <i>Hamartomatous polyposis</i>
Juvenile polyposis
Cowden disease
Ruvalcaba–Myhre–Smith syndrome
Peutz–Jeghers syndrome
Gorlin syndrome
McCune–Albright syndrome
Cronkhite–Canada syndrome
Tuberose sclerosis (few, rectal polyps)
Hereditary mixed polyposis syndrome
DICER1 syndrome (usually few in number)
3. <i>Inflammatory polyps</i>
Inflammatory bowel disease
Devon polyposis
4. <i>Ganglio/neurofibromata</i>
Neurofibromatosis type 1
MEN 2B
Cowden
5. Hyperplastic polyposis (now usually referred to as serrated polyposis)

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<sup>a</sup>CMMRD – constitutional mismatch repair deficiency

## Gastrointestinal Polyposis

Disorders associated with gastrointestinal polyposis may be classified according to the histological type of the polyps (Hodgson and Murday 1994; see Table 5.2). Adenomatous polyps occur in familial adenomatous polyposis (p. 241), Turcot syndrome (p. 311), MUTYH-associated polyposis (Sampson et al. 2009; Vogt et al. 2009; p. 287), in those with POLE or POLD1 mutations (Palles et al. 2013) and in Lynch syndrome and biallelic MMR mutation carriers (p. 232) and occasionally in Cowden syndrome (p. 233). Hamartomatous polyps occur in Peutz–Jeghers syndrome (p. 299), juvenile polyposis (p. 267) (Hyer et al. 2000; Zhou et al. 2001; Erdman and Barnard 2002), and the hereditary mixed polyposis syndrome (HMPS) (Whitelaw et al. 1997) caused by a single founder *GREM1* mutation (Jaeger et al. 2012), Cowden syndrome (p. 233) (Gentry et al. 1978; Eng et al. 2003), Ruvalcaba–Myhre syndrome (p. 221), McCune–Albright syndrome, and occasionally in Gorlin syndrome. The Cronkhite–Canada syndrome, characterized by hamartomatous (juvenile) polyps throughout the whole intestine and associated with alopecia, onychodystrophy, and abnormal pigmentation of adult onset, is probably not genetic (Daniel et al. 1982) but does predispose to CRC (Zugel et al. 2001).

Almost 50 % of cases of juvenile polyposis are due to germline mutations in *SMAD4* or *BMPRIA*, which encode proteins involved in TGF  $\beta$  signaling (Houlston et al. 1998; Howe et al. 2001; Sayed et al. 2002). There is a significant risk of colorectal malignancy in juvenile polyposis and Peutz–Jeghers syndrome. Ganglioneuromatous polyposis may occur in Cowden syndrome, and adenomas and hamartomas may also arise, with malignant potential (Trufant et al. 2011).

Hereditary mixed polyposis syndrome causes an autosomal dominant predisposition to colorectal polyps of varying histological type including sessile, hamartomatous, and adenomatous polyps and early-onset CRC. The locus for the susceptibility gene has been identified as *CRAC1* on chromosome 15q in Ashkenazi Jewish families, and the responsible gene, *GREM1*, has now been identified. Thus far, only one founder mutation (in the AJ population) is known to exist (Jaeger et al. 2012).

Small rectal hamartomatous polyps have recently been described in tuberose sclerosis (p. 307), but these are thought to be of no clinical significance (Gould et al. 1990). Inflammatory polyps are associated with ulcerative colitis and Crohn's disease. Gastrointestinal hamartomatous polyps have been noted in those with germline *DICER1* mutations (Foulkes et al. 2011). Gastrointestinal polyps, predominantly neurofibromas, are found in NF1 (p. 288), possibly in up to 25 % of cases (Hochberg et al. 1974; Cooney and Jewell 2009). A diffuse ganglioneuromatosis of the gastrointestinal tract is described in MEN 2B (p. 281), with hyperplasia of the ganglion cells, leading to malfunction of the bowel (Fryns and Chrzanowska 1988). Rarely, autosomal dominant inheritance of intestinal neurofibromatosis has been described without other associated manifestations of neurofibromatosis (Heiman et al. 1988).

The juvenile polyps in individuals with McCune–Albright syndrome show some similarities to those seen in PJS, and activating mutations in *GNAS* have been detected in the polyps. Affected individuals may also have perioral freckling (Zacharin et al. 2011). The Cronkhite–Canada syndrome, characterized by hamartomatous (juvenile) polyps throughout the whole intestine and associated with alopecia, onychodystrophy, and abnormal pigmentation of adult onset, is probably not genetic, but does predispose to CRC (Zugel et al. 2001; Sweetser et al. 2012). Devon polyposis has been described in one family in which multiple inflammatory fibroid polyps were found in the upper gastrointestinal tract in members of three generations of a family from Devon, UK. There did not seem to be an increased risk of cancer in these individuals (Anthony et al. 1984; Allibone et al. 1992).

## Tumors of the Colon and Rectum

Malignant disease of the large bowel is one of the commonest causes of cancer death, with an incidence of 32 per 100,000 population in the UK, but a much lower incidence in parts of Africa (2.5 per 100,000 in Nigeria) and in Asia. Almost all (98 %) large bowel cancers are adenocarcinomas. Adenomas of the colon are thought to have the potential to develop into malignancy and coexist in 75 % of cases in which more than one primary carcinoma is present in the colon; one or more adenomas are present in about a third of cases of colon carcinoma. It is thus probable that most

**Table 5.3** Family history and risk of death from colon cancer: empiric risk estimates for counseling

Affected relatives	Relative risk of CRC	Lifetime risk of CRC
General population		1 in 50
One first-degree relative	×3 (OR 1.8)	1 in 17
One first degree aged <45 years	×5 (OR 3.7)	1 in 10
One first and one second degree		1 in 12
Both parents		1 in 8.5
Two first-degree relatives	(OR 5.7)	1 in 6
Three first-degree relatives		1 in 3

Odds ratio (OR) figures from St John et al. (1993); lifetime risks from Houlston et al. (1990)

carcinomas develop from adenomas (Morson 1966). The incidence of solitary colonic polyps in the general population is age-related, reaching 34 % in the sixth decade and 75 % in those over the age of 75 years (Lanspa et al. 1990; Dunlop 2002; Fletcher 2008). It has been calculated that the risk of invasive cancer in a single polyp is approximately 0.25 % per year, but for larger and/or villous polyps, the risks are up to 50 times higher (Eide 1986), indicating that screening guidelines need to be modified by the pathological findings at each colonoscopy. Inflammation is probably also a predisposing factor for bowel cancer, since ulcerative colitis and Crohn's disease are associated with an increased risk of colon carcinoma (Judge et al. 2002). The risk of colorectal cancer in these conditions is similar for a similar extent and duration of colonic involvement, and surveillance guidelines have been developed for individuals with inflammatory bowel disease (Eaden and Mayberry 2002; Cairns et al. 2010). Individuals with acromegaly also have an increased prevalence of colorectal adenomas and cancers, RR 7.4, prevalence 3.7 % overall (Jenkins and Besser 2001).

Genetic factors are important in the pathogenesis of cancer, and a comprehensive family history should be part of the assessment of all patients with CRC. Early age at diagnosis in the affected relative is an important predictor of risk. Empiric risk estimates based on the number of relatives affected by (and age at diagnosis of) CRC are given in Table 5.3 and indicate that risk increases with earlier age at diagnosis and increased numbers of affected relatives. Twin studies indicate that 35 % of CRCs are partly due to inherited factors (Lichtenstein et al. 2000). Identification of individuals at increased genetic risk of colon cancer is important because screening can be offered to high-risk individuals, and evidence is accumulating that this is likely to be effective in reducing morbidity and mortality from CRC.

It is estimated that about 5 % of CRCs occur in individuals with a dominantly inherited predisposition. Genetic conditions associated with colonic polyps carry an increased risk of CRC (Table 5.4). These include familial adenomatous polyposis (p. 241), juvenile polyposis (p. 267), and Peutz–Jeghers syndrome (p. 299). Familial adenomatous polyposis is characterized by the development of colorectal adenomas, whereas the latter conditions are characterized by gastrointestinal hamartomas, which are potentially premalignant although adenomas have more malignant potential. A rare familial syndrome of familial giant hyperplastic polyposis coli has been described which predisposes to CRC (Jeevaratnam et al. 1996;

**Table 5.4** Conditions characterized by colorectal polyposis

Condition	Gene
<i>Adenomatous polyposis</i>	
Familial adenomatous polyposis (FAP)	<i>APC</i>
Attenuated polyposis/multiple adenomas	<i>APC, MUTYH, POLE, POLD1, MMR</i> genes
<i>Hamartomatous polyposis</i>	
Juvenile polyposis	<i>BMPRIA, SMAD4, ENG, STK11</i>
Peutz–Jeghers syndrome	<i>LKB1/STK11</i>
Cowden syndrome	<i>PTEN</i>
Hereditary mixed polyposis syndrome	<i>GREM1</i>

Sheikholeslami et al. 2004). More recently, the importance of some types of hyperplastic polyps, particularly as precursors of right-sided microsatellite unstable colon cancers, has been stressed (Jass et al. 2002). Conditions predisposing to gastrointestinal polyps are listed above (Ngeow et al. 2013; p. 62).

Germline *PTEN* mutations are also associated with hamartomatous gastrointestinal polyps, but unlike the genes listed above, mutation carriers (affected with Cowden or Ruvalcaba–Myhre–Smith syndromes) do not seem to have a greatly increased risk of CRC, but there may be some risk in specific families.

Familial adenomatous polyposis is the most common of these disorders but accounts for fewer than 1 % of all cases of colon cancer. A larger proportion of colon cancer (probably 2–3 %) is accounted for by Lynch syndrome (HNPCC) (Evans et al. 1997; Salovaara et al. 2000), an autosomal dominant inherited predisposition to CRC (p. 256), in which bowel cancers occur with high frequency at an early age (on average two decades earlier than sporadic cases). Mutations in one of several genes involved in the repair of DNA mismatch errors (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) have been found to cause Lynch syndrome, and microsatellite instability (MSI) is seen, where multiple allelic changes are demonstrable in tumor DNA when compared to the constitutional DNA of the patient. The condition predisposes to early-onset tumors with increased proportion of right-sided colon cancers (65 % versus 25 % in sporadic cases), and a risk of multiple primary CRC. The risk of extracolonic cancers is higher in individuals with *MSH2* than *MLH1* mutations (Vasen et al. 2001; Bonadona et al. 2011), and *MSH6* mutations particularly predispose to endometrial cancer (Wijnen et al. 1999). These extracolonic malignancies comprise mainly endometrial, ovarian, pancreatic, gastric, and urinary tract cancers (Wijnen et al. 1999). Full details of Lynch syndrome are given on page 249. Muir–Torre syndrome is Lynch syndrome associated with sebaceous adenomas and other characteristic skin lesions, and they are allelic (i.e., due to mutations in the same gene), but Muir–Torre syndrome has generally been considered to be due to mutations in *MSH2* rather than *MLH1* (Lucci-Cordisco et al. 2003). Biallelic MMR mutation carriers are at significantly increased risk of very early-onset colorectal cancer (Herkert et al. 2011).

Germline mutations in *MLH3* and *EXO1* may account for a small proportion of CRC cases with MSI-positive tumors (Wu et al. 2001; Niessen et al. 2009; Liu et al. 2003; Laiho et al. 2002; Brassett et al. 1996; Sutter et al. 2004). Clinically important mutations in these genes are exceptionally rare.

Germline deletions of the last exons of *EPCAM*, the gene directly upstream of *MSH2*, result in loss of *MSH2* expression by methylation of the promoter, and thus testing for *EPCAM* deletions is essential if IHC shows loss of *MSH2*, and yet no coding sequence or MLPA-identified mutation is found in *MSH2* (Kuiper et al. 2011). Interestingly, such mutations are associated with a lower risk of endometrial cancer (Ligtenberg et al. 2013; Charbonnier et al. 2002).

The estimated cumulative risks of colorectal cancer by 70 years of age in individuals with Lynch syndrome have recently been reported as 41 % (95 % confidence intervals [CI], 25–70 %) for *MLH1* mutation carriers, 48 % (95 % CI, 30–77 %) for *MSH2*, and 12 % (95 % CI, 8–22 %) for *MSH6* (Hampel et al. 2006). For endometrial cancer, corresponding risks were 54 % (95 % CI, 20–80 %), 21 % (95 % CI, 8–77 %), and 16 % (95 % CI, 8–32 %). For ovarian cancer, they were 20 % (95 % CI, 1–65 %), 24 % (95 % CI, 3–52 %), and 1 % (95 % CI, 0–3 %). The estimated cumulative risks by age 40 years did not exceed 2 % (95 % CI, 0–7 %) for endometrial cancer or 1 % (95 % CI, 0–3 %) for ovarian cancer. The estimated lifetime risks for other tumor types did not exceed 3 % with any of the gene mutations (Bonadona et al. 2011). These risks are lower than those published previously.

The term hereditary non-polyposis colon cancer (HNPCC) is something of a misnomer (Umar et al. 2004), since colonic adenomas do occur in patients with this condition; thus, the name Lynch syndrome has generally replaced HNPCC in common usage (Vasen et al. 1999). Although colonic adenomas are not more common in Lynch syndrome than in the general population, the adenomas progress more rapidly through the adenoma–carcinoma sequence than in normal individuals (Jass 1995a, b). This has implications for the frequency with which colonoscopic surveillance should be performed in these individuals. It is very rare for more than 50 polyps to develop in this condition, which distinguishes it from classical familial adenomatous polyposis in which there is a minimum of 100 colonic adenomas. There are, however, families with intermediate numbers of polyps that cannot easily be classified as Lynch syndrome or familial adenomatous polyposis (sometimes known as attenuated familial adenomatous polyposis, AFAP, or AAPC), and affected individuals in some such families may be demonstrated to have germline mutations in exons 3 or 4 of the *APC* gene (Spirio et al. 1993; Gismondi et al. 2002). Others may have *MUTYH*-associated polyposis, an autosomal recessive condition characterized by variable numbers of colonic adenomas and relatively early-onset CRC, with usually 30–100 adenomas (Halford et al. 2003; see p. 287). Very recently, rare mutations in *POLE* and *POLD1* have been identified in families with multiple colorectal adenomas and associated carcinomas. The families may resemble AFAP families in some respects (Palles et al. 2013). A subgroup of Lynch syndrome-related CRC may be distinguished by the occurrence of flat adenomas in the right hemicolon (Lynch et al. 1993), but it seems likely that this is merely another variant of Lynch syndrome. However, serrated adenomas are common in HMPS (hereditary mixed polyposis syndrome), characterized by colonic adenomas and hamartomas and early-onset CRC, caused by a single germline deletion in *GREM1* (Jaeger et al. 2012).

The prevalence of pathogenic *APC* and biallelic *MUTYH* mutations was 80 % and 2 %, respectively, among individuals with 1,000 or more adenomas, 56 % and 7 % among those with 100 to 999 adenomas, 10 % and 7 % among those with 20 to 99 adenomas, and 5 % and 4 % among those with 10 to 19 adenomas in a recent study, so *APC* mutations predominated in patients with classic polyposis, whereas

prevalence of *APC* and *MUTYH* mutations was similar in attenuated polyposis (Grover et al. 2012).

A polymorphism in the *APC* gene, a T-A mutation germline mutation (predicted to result in a change from isoleucine to lysine position 1,307 of the protein; see familial adenomatous polyposis section, p. 241), confers an approximately twofold increase in the risk of CRC. The mechanism for this at a molecular level appears to be that the polymorphism, which converts an AAATAAAA sequence to (A)<sub>8</sub>, predisposes to the development of somatic mutations in the *APC* gene (Laken et al. 1997). This mutation is common (about 6 %) in individuals of Ashkenazi Jewish origin, but is very rare in other ethnic groups. The relative risk or odds ratio for CRC in association with this mutation is about 1.5–1.8 (Gryfe et al. 1999), which is generally thought to be insufficient to warrant colonoscopic surveillance. The mutation is at least 2,200 years old (Niell et al. 2003) and has probably become frequent in this population by genetic drift.

There is possibly a slightly increased relative risk of colon cancer in individuals with germline *BRCA1* mutations, but this is accompanied by a decrease in risk for rectal cancer, and this increased risk has not been reported in men (Thompson and Easton 2002). Overall, the risks are probably not clinically important. In support of the absence of an effect, there is no apparent increased risk for CRC for Ashkenazi Jewish carriers of *BRCA1:185delAG* or *BRCA1:5382inC* (Ford et al. 1995; Struewing et al. 1997; Kirchhoff et al. 2004; Niell et al. 2004).

NAT2 (which alters the ability to acetylate N-acetyl transferase) and other metabolic gene variants may alter susceptibility to colonic adenomas and cancer in the general population and alter polyp density in FAP (Crabtree et al. 2002; Jass 2004), but are unlikely to cause a sufficiently increased CRC risk to be clinically important on their own. It may be that multiple variants in different genes including *MLH1*, *MSH2*, *APC*, *AXIN1*, and *CTNGB1* (beta catenin) can contribute to susceptibility to colonic adenomas and cancer (Fearnhead et al. 2004; Lammi et al. 2004), but none of these loci are clinically useful.

## Identification of High-Risk Families

Efficient screening for Lynch syndrome requires that high-risk individuals are targeted for mutation testing. Approximately 10 % of patients with CRC have an affected first-degree relative, and 2 % have two affected first-degree relatives. However, the frequency of families that fulfill the “Amsterdam Criteria” (AC) for Lynch syndrome is less than 5 % of all cases (Stephenson et al. 1991; Peel et al. 1997). The Bethesda criteria are more sensitive but less specific (Umar et al. 2004). Most population-based mutation analysis studies start with individuals with microsatellite unstable cancers and then look for germline mutations in these cases only: these studies have found that between 1 and 4 % of all CRC is due to germline mutations in either *MLH1* or *MSH2* (Peel et al. 2000; Salovaara et al. 2000) (Table 5.5). Some patients with early-onset CRC with no family history still have germline mutations in the mismatch repair genes (Dunlop et al. 1997), and these may account for a substantial proportion of CRC in patients diagnosed below 35 years, but only a minority of older cases. Persons

**Table 5.5** Frequency of germline *MLH1* and *MSH2* mutation carriers in early-onset CRC

Age range (years)	Number of index cases	<i>MLH1</i> mutation carriers		<i>MSH2</i> mutation carriers	
		Number	%	Number	%
<30	50	7	14	7	14
<40	12	1	8.3	1	8.3
<45	38	1	2.6	2	5.3
<50	135	6	4.4	6	4.4

with CRC caused by germline *MSH6* mutations often do not fulfill either AC1 or AC2 (Sjursen et al. 2010).

In families not fulfilling the Amsterdam or Bethesda criteria for Lynch syndrome (see p. 258, Tables 11.4, 11.5, 11.6), pathological tumor analysis by immunohistochemical stains (IHC) gives a high specificity for the diagnosis of Lynch syndrome and indicates the gene which may be mutated in the germline, although *MSH2* and *MSH6* staining may both be lost in tumors in people with germline mutations in *MSH2*. Measurement of MSI in tumors is less specific because approximately 15 % of all CRCs may be MSI positive and does not indicate which gene is likely to be involved in the germline. Some cases, especially older women with MSI-high cancers, may have somatic *MLH1* inactivation. The specificity of MSI for Lynch syndrome is increased considerably if two tumors from the same individual demonstrate MSI positivity (Vasen 2007; Lubbe et al. 2009; EGAPP Recommendation Statement 2009; Tresallet et al. 2012; Parsons et al. 2012).

In terms of identifying individuals at risk, it should be remembered that some patients with early-onset CRC without a family history of Lynch syndrome have germline mutations in mismatch repair genes (Dunlop et al. 1997; Hampel et al. 2005). If cases of CRC unselected for family history are studied for mismatch repair gene mutation analysis, the mutation detection rate is dependent on the age at diagnosis of CRC in the case (Mitchell et al. 2002; see Table 5.5). Familial clustering of CRC that does not fulfill the AC for a diagnosis Lynch syndrome is less likely to be due to germline *MLH1* or *MSH2* mutations. In early studies, only about 8 % of families not meeting the rather stringent AC1 had detectable mutations although some may have deletions or other gene rearrangements (Wijnen et al. 1997). This may be an underestimate, and detailed searches can find mutations in many more, as long as MSI-H is present in the CRC of the subject of the mutation analysis (Wagner et al. 2003), and would be considered to be very likely if *MSH2* protein is absent, even if the family clustering in no way fulfills AC. In this context, looking for *BRAF* mutations (Davies et al. 2002) in the colorectal tumor may be a good step following MSI and IHC, as among MSI-H cancers that do not express *MLH1*, the presence of a *BRAF* mutation makes a germline *MLH1* mutation much less likely. Interestingly, loss of expression of *MSH2* is rarely if ever associated with *BRAF* mutations (Wang et al. 2003; Koinuma et al. 2004; Domingo et al. 2004). More recent publications have presented improved algorithms for testing tumors in newly diagnosed cases of CRC, stratified by age at diagnosis and family history, and in general MSI analysis is performed initially, as it is more sensitive but less specific than IHC, and then IHC performed to indicate the most likely gene involved. IHC can be a first step in cases



conforming to the Bethesda criteria for Lynch syndrome (Lubbe et al. 2009; Halbert et al. 2004; Hampel 2010; Hall 2010; Rodriguez-Bigas et al. 1997; Parsons et al. 2012; Steinhagen et al. 2012; Tresallet et al. 2012).

## Pathological Features

Colorectal cancers with MSI-high features characteristically have increased mucin secretion, differentiation, and lymphocytic infiltrate. This is seen both in sporadic tumors and those arising in Lynch syndrome. There is now evidence that sporadic MSI-H cancers develop in adenomas with a somatic *BRAF* mutation and DNA methylation, particularly of *MLH1*, while those in Lynch syndrome arise in adenomas with somatic mutations in *APC*, beta catenin, and/or *KRAS*. This also translates into morphological differences, Lynch syndrome-associated cancers showing more tumor budding (de-differentiation), and sporadic tumors being more heterogeneous and displaying mucin secretion (Jass 2004; McGivern et al. 2004).

Molecular genetic studies of colon cancer have provided strong evidence for a multistep pathogenesis. This work started out with a simple linear model involving at least five genes (Fearon and Vogelstein 1990). Although this model is too simplistic, it has provided a framework for many other studies. *APC* mutations are thought to occur early in the process and may cause spindle aberrations via the interaction of *APC* with the kinetochore at mitosis through connections with the microtubules, leading to chromosome abnormalities (Powell 2002). Originally, it was thought that the critical factor is the accumulation of mutations rather than the particular order in which they occur, but more recent work, focusing on the idea of cell-type-specific “gatekeepers,” suggests that there are genes which act as rate-limiting steps: it is likely that such genes are altered early in the carcinogenetic process. For example, in most CRC, biallelic *APC* mutations (or mutation plus loss of heterozygosity) occur at an early stage (Powell et al. 1992). These early alterations (such as the loss of sequences C-terminal to the beta catenin regulatory domain (Sidransky 1997)) could lead to a screening test for early CRC based on the detection of such mutations in stool. A stool test for *APC* mutations was developed (Traverso et al. 2002) but has not been taken up commercially, and it is not in widespread use. Other assays are based on multiple genes: for example, stool analysis of three gene markers (*TP53*, *BAT26*, and *KRAS*) detected 71 % of CRC patients and 92 % of those whose tumors actually had an alteration in these genes (Dong et al. 2001). Despite these and other encouraging findings, commercial molecular-based stool tests remain unadopted in the clinical setting.

## Surveillance Strategies

Screening of patients at increased risk of colon cancer is likely to prevent early death, but large-scale studies are of course difficult to conduct. In Finland, one study has found that Lynch syndrome family members who undergo colonoscopy have a



much lower CRC incidence rate, probably due to removal of adenomas. The overall death rates were 10 versus 26 subjects in the study and control groups ( $P = 0.003$ ) and 4 versus 12 in mutation-positive subjects ( $P=0.05$ ) (Jarvinen et al. 2000). In addition, the benefits of a genetic register for ascertaining and coordinating the screening of individuals at risk for familial adenomatous polyposis are now well recognized (Kinzler and Vogelstein 1996; King et al. 2000; Vasen et al. 2008).

In a significant proportion (approximately 30 %) of families that meet the Amsterdam criteria, the results of the MSI and IHC analysis of the colorectal tumor(s) are negative. Clustering of CRC by chance or genetic factors other than Lynch syndrome may be responsible for the disease in these families, which are characterized by a more advanced age of onset of CRC than in families with Lynch syndrome, and the absence of endometrial cancer and multiple tumors. The risk of developing CRC in such families is increased only by a factor of 2.3, so a less-intensive colonoscopic surveillance program (e.g., colonoscopy every 5 years, starting 5–10 years before the first diagnosis of CRC or at 45 years) might be appropriate (Vasen et al. 2007, 2009; Järvinen et al. 2008). The close relatives of those found to have no evidence of Lynch syndrome, but where there is a family history of later-onset CRC, have a higher CRC risk where the CRC is microsatellite unstable (Aaltonen et al. 2007).

Predictive testing for Lynch syndrome is now available for the presymptomatic diagnosis of this condition in families in which the pathogenic mutation has been defined, so that it is becoming possible to target high-risk asymptomatic individuals for screening, as for familial adenomatous polyposis. Guidelines for screening individuals at risk for Lynch syndrome are regular colonoscopy (every 1–2 years) from the age of 25 years, and those with a family history that includes cancers at other sites, including endometrium, should be offered screening for other cancers as appropriate (Vasen et al. 2010a, b; see p. 256). In addition to detecting presymptomatic colonic carcinomas, such screening allows the endoscopic detection and removal of adenomas. It is presumed (but not proven) that most cancers in patients with Lynch syndrome arise from adenomas and that excision of the latter will prevent the development of colon cancer. Colonoscopy is the investigation of choice because of the preponderance of right-sided tumors in this condition (Vasen et al. 2013).

In familial CRC families without evidence for Lynch syndrome, surveillance for CRC should take into account the financial costs of screening and the possibility of adverse effects of screening by colonoscopy in particular and balance this with the individual's estimated risk of CRC (Johnson et al. 2008). Cairns et al. (2010) have published family history criteria for individuals at high–moderate and low–moderate risk of developing colorectal cancer based on the polygenic inheritance model and have advocated screening protocols based on these groupings. Briefly, individuals assessed as being at high–moderate risk may have three affected relatives at any age, in a first-degree kinship, or two affected relatives diagnosed below 60 years of age. Individuals at low–moderate risk would be those with one affected relative diagnosed before 50 years of age or two diagnosed over the age of 60 years of age. They advocated that the high–moderate risk group should have 5 yearly colonoscopies from 50 years of age and the low–moderate risk group one colonoscopy at 55 years of age, and no further investigations unless polyps were detected at the screening colonoscopy (Table 5.6). These guidelines for screening in those at moderately

**Table 5.6** Screening guidelines for colon cancer in individuals with a moderate family history of CRC: a guide for the gastroenterologist and colorectal surgeon

CRC in 3 FDR in 1st-degree kinship, none diagnosed <50 years of age	Colonoscopy 5 yearly	From 50 to 75 years of age
CRC in 2 FDR in 1st-degree kinship, mean age <60 years of age	Colonoscopy 5 yearly	From 50 to 75 years of age
CRC in 2 FDR diagnosed >60 years of age	Single colonoscopy	Once at 55 years of age; no more if normal
CRC in 1 FDR diagnosed <50 years of age	Single colonoscopy	Once at 55 years of age; no more if normal
Other FH CRC unless diagnostic of Lynch	No screening	
Amsterdam criteria positive	Refer to genetics center	
Incident CRC cases diag. <50 years of age or MSI+, not Amsterdam criteria positive	Arrange MSI/IHC, consider referral to genetics center	
FAP/MUTYH polyposis	Refer to genetics center	

Adapted from Cairns et al. (2010)  
FDR first-degree relative, SDR second-degree relative

increased risk of CRC as assessed by family history have been updated in the UK, commissioned by the British Society of Gastroenterology and the Association of Coloproctology for Great Britain and Ireland, based on literature review and expert opinion (Cairns et al. 2010). They take into account the fact that the risks of colonoscopy are small but significant (Williams and Fairclough 1991); in a population-based study, serious complications were recorded in 2 per 1,000 colonoscopies (Gatto et al. 2003). The 14-day death rate is around 5–10 % of the perforation rate, or 0.83 per 10,000 procedures (CI 0.025–3.69), and 3.9 per 10,000 (CI 1.1–8.8) after polypectomy (Anderson et al. 2000; Gatto et al. 2003). The perforation rate after polypectomy is quoted as 22 (CI 13.8–33.3) per 10,000, with post-polypectomy bleeding in a further 89 (CI 71.5–109.5) per 10,000 (Cairns et al. 2010; Zha et al. 2004; Imperiale et al. 2008).

Some newer forms of colonoscopic surveillance in Lynch syndrome have been advocated but are not yet in widespread use (Haanstra et al. 2013).

Chemoprophylaxis

There had been anecdotal evidence that COX-2 inhibitors could reduce the development of colonic neoplasia in susceptible individuals for some year, so aspirin and nonabsorbable starch were assessed in large-scale trials (the Concerted Action Polyp Prevention [CAPP] studies). In CAPP2, no preventive effect of starch was noted (Mathers et al. 2012). When individuals with Lynch syndrome were treated with 600 mg/day of aspirin for over 25 months, the risk of CRC was significantly reduced at almost 5 years follow-up (Burn et al. 2011a, b; Evans et al. 2012). No

effect was seen for Lynch syndrome mutation carriers in an earlier analysis of the same study (Burn et al. 2008), suggesting that the preventive effect associated with aspirin use is delayed and prolonged. Larger trials are planned, and finding the optimal dose will be the next step. In FAP, the CAPP1 study showed that aspirin had a modest effect on polyp progression, but no effect on polyp number (Burn et al. 2011a, b) – but in view of the delayed effect seen in the later analysis of CAPP2, perhaps a long-term follow-up study will show benefit. Fish oils have long been thought to be protective against GI cancers, and a special formulation of eicosapentaenoic acid (EPA) was able to reduce polyp number and size (West et al. 2010).

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## Chapter 6

# Reproductive System

### Breast Cancer

#### *Background: Epidemiology and Family History*

Breast cancer is the most common non-cutaneous cancer in women, accounting for 20 % of all new cases of cancer. The lifetime risk of breast cancer in the UK is one in nine females, with an annual incidence of <10 per 100,000 women aged <30 years, rising to 300 per 100,000 in women aged over 85 years. Similar, but slightly higher rates are seen in North America. It is rare in men (<1 per 100,000). Breast cancer incidence shows marked geographical variation: it is much less common in Asian than in Caucasian women and less frequent in South America and Spain than in Northern Europe, North America, and Australia. In India, the prevalence is lower (although rising) among most ethnic groups. In North America, the incidence of breast cancer appears to have increased in recent years; most of this increase is due to mammographic detection of ductal carcinoma in situ leading to early diagnosis of minimally invasive ductal carcinoma. It is notable that the rates of breast cancer to age 40 are fairly stable around the globe (Narod 2012a). Nearly all the differences in incidence from country to country occur in women diagnosed above this age, and it is even more noticeable in women diagnosed in the postmenopausal years (Leong et al. 2010), suggesting that nongenetic factors predominate in women diagnosed at older ages. Because the known highly penetrant breast cancer susceptibility genes cannot explain most of the diagnoses of breast cancer in women diagnosed under 40 years of age (they are clearly highly “genetic”), other genetic mechanisms must be at play.

In 1948, Penrose and colleagues observed that breast cancer may have a hereditary basis in some families (Penrose et al. 1948). A genetic influence on breast cancer susceptibility is suggested by twin studies, as the concordance for breast cancer in identical twins (0.28) is more than twice that in dizygotic twins (0.12). A statistically significant heritable factor of 27 % was observed for breast cancer (95 % confidence interval (CI): 4–41) in the three-country study of 44,788 pairs of twins (Lichtenstein et al. 2000). By contrast, the factor for prostate cancer was

42 %, so clearly these percentages do not reflect the contribution of highly penetrant genes to these diseases.

There is an increased risk of breast cancer among female relatives of breast cancer patients and this increased relative risk (RR) is more pronounced when the index case has bilateral disease or early (premenopausal) age at onset. For patients 55 years of age or older at diagnosis, the RR of breast cancer in a first-degree female relative is approximately 1.8, increasing to 3–4 when more than one first-degree relative is affected. A large study (7,496 women with breast cancer and 7,438 controls) of the risks of breast cancer in women in relation to their family history found that, compared to women with no affected relative, the risk ratio for breast cancer was 1.80 (99 % CI 1.69–1.91), 2.93 (99 % CI 2.30–3.64), and 3.90 (2.03–7.49), respectively, for one, two, and three or more affected first-degree relatives ( $P < 0.0001$  each) (Collaborative Group on Hormonal factors in breast cancer 2001). Risk ratios were greatest at young ages, and with younger age at diagnosis in the relative. For women with zero, one, or two or more first-degree affected relatives, the estimated cumulative risk of breast cancer up to age 50 years was 1.7, 3.7, and 8 %, respectively, corresponding to incidences up to age 80 of 7.8, 13.3, and 21.1 %, and death from breast cancer of 2.3, 4.2, and 7.6 %. There was no evidence for an autosomal recessive effect. An important finding was that other factors such as hormones and diet did not vary by family history.

Among women with one affected relative, the cumulative incidence of breast cancer between ages of 20 and 80 was 12.3 % if the relative was over 60, but 16.1 % if under 40. Another key finding was that most breast cancers in women with a family history of breast cancer were likely to occur after the age of 50, even if there were two affected relatives (Collaborative Group on Hormonal factors in breast cancer 2001).

For a woman aged 30 with a mother and a sister affected with breast cancer, the cumulative risk of breast cancer to age 70 has been found to be 17.4 %, significantly lower than the 43 % risk to be expected if all such familial clusters were due to highly penetrant mutations in susceptibility genes (Peto et al. 1996), suggesting that most such familial clusters are not due to these genes.

There is epidemiological evidence for overlap between breast and ovarian cancer susceptibility. The overall age-adjusted RR for ovarian cancer in first-degree relatives of women with breast cancer has been estimated to be 1.7 (and 2.1 for breast cancer), and first-degree relatives of index cases of ovarian cancer have RR of 1.6 and 2.8 for breast cancer and ovarian cancer, respectively. In one study, the RR for breast cancer in first-degree relatives of index cases ascertained because of colon cancer was estimated to be about 5, but in general, later studies of the risk of breast cancer after colorectal cancer, or colorectal cancer after breast cancer, have not supported this finding (Newschaffer et al. 2001). The only gene that might reasonably contribute to both breast and colorectal cancer in this context is *CHEK2* (Meijers-Heijboer et al. 2003), but this is probably only clinically relevant in the Netherlands and possibly Finland. It is possible that some “breast/colorectal” families are due to mutations in two genes, with one responsible for breast cancer, and the other for colorectal cancer (Thiffault et al. 2004). It should be noted that recent prospective studies have suggested an up to fourfold increase in breast cancer for patients

**Table 6.1** RR estimates (95 % floated CI) for mutation carriers, in BRCA1 and BRCA2

Age group	<i>BRCA1</i>		<i>BRCA2</i>	
	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer
20–29 years	18 (4.4–75)	1.0	19 (4.4–82)	1.0
30–39 years	36 (25–52)	38 (17–88)	16 (9.3–29)	1.0
40–49 years	31 (25–52)	61 (38–99)	9.5 (5.9–15)	6.3 (1.4–28)
50–59 years	16 (9.6–27)	30 (14–65)	11 (6.6–17)	19 (9.1–41)
60–69 years	11 (5.0–25)	48 (22–109)	9.2 (5.1–17)	7.3 (1.8–30)

Table based on country and cohort-specific background rates (Antoniou et al. 2003)

carrying germline mismatch repair gene mutations (Win et al. 2012) (see p. 256, Chap. 5 Lynch syndrome).

BRCA1 and BRCA2

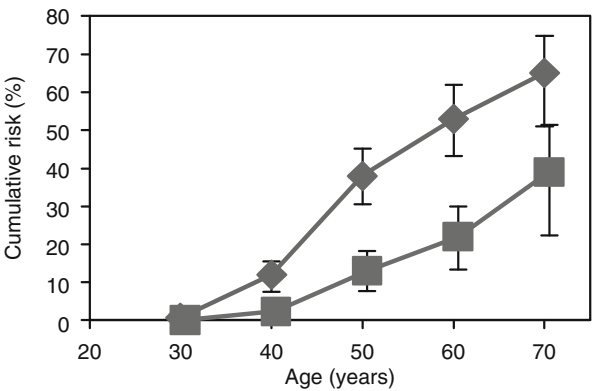
The Genes and the Risks for Cancer

Twenty years after they were first discovered, *BRCA1* and *BRCA2* remain the two most important breast cancer susceptibility genes, by some considerable margin (Narod 2012b). *BRCA1* on chromosome 17q12–23 accounts for most families with inherited breast and ovarian cancer susceptibility and about 40 % of inherited breast cancer, particularly where the onset of breast cancer was at 45 years or younger (Figs. 6.1 and 6.2).

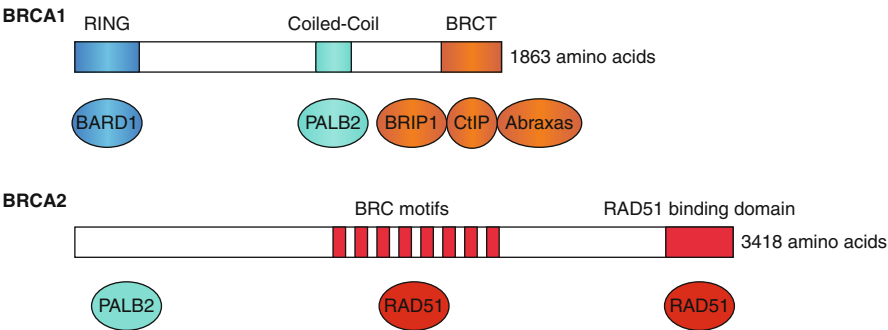
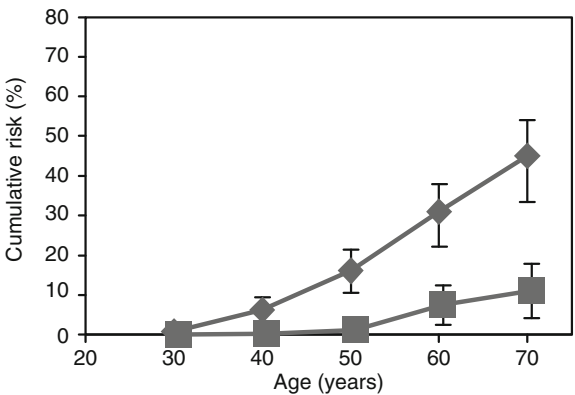
*BRCA2*, located on chromosome 13q, was identified a year later. Germline mutations in this gene confer a strong susceptibility to breast cancer and a smaller risk of ovarian cancer than with *BRCA1* mutations. Gene penetrance for lifetime risk of breast cancer in *BRCA2* mutation carriers is lower than in the case of *BRCA1* mutations and results in later-onset disease: in cases unselected for family history, the average cumulative risks for breast cancer in *BRCA1* mutation carriers by age 70 years was 65 % (95 % CI 44–78 %). In *BRCA2* carriers, the estimate was 45 % (31–56 %) (Figs. 6.1 and 6.2).

Relative risks (RR) are shown in Table 6.1, and age-dependent penetrance is shown in Fig. 6.1 (*BRCA1*) and Fig. 6.2 (*BRCA2*) (Mavaddat et al. 2013). Mutations in *BRCA2* predispose to a wider spectrum of other cancers than do mutations in *BRCA1*. These cancer sites include prostate, stomach, pancreatic, and male breast cancers (Couch et al. 1997). In this large international study, statistically significant increases in risks were observed for prostate cancer (Table 6.2) (estimated RR=4.65; 95 % CI: 3.48–6.22), pancreatic cancer (RR=3.51; 95 % CI: 1.87–6.58), gallbladder and bile duct cancer (RR=4.97; 95 % CI: 1.50–16.52), stomach cancer (RR=2.59; 95 % CI: 1.46–4.61), and malignant melanoma (RR=2.58; 95 % CI: 1.28–5.17). The RR for prostate cancer for men below the age of 65 years was 7.33 (95 % CI: 4.66–11.52). There was a significant reduction in risks for women in earlier birth cohorts.

**Fig. 6.1** Cumulative incidence of breast cancer (diamonds) and ovarian cancer (squares) in BRCA1-mutation carriers, to age 70. From Antoniou et al. 2003, with permission



**Fig. 6.2** Cumulative incidence of breast cancer (diamonds) and ovarian cancer (squares) in BRCA2-mutation carriers, to 70 age



**Fig. 6.3** BRCA1 and BRCA2 and binding partners (color-coded with corresponding interacting domain). BRCA1 consists of 1863 amino acids and contains three functionally important domains: a RING-finger domain which binds to BARD1 mediating ubiquitination of various proteins involved in chromosome stability, a coiled-coil domain which binds to PALB2 bridging it to BRCA2, and a BRCT domain which binds to phosphorylated proteins such as the protein complex, Abraxas-CtIP-BRIP1, regulating homologous repair. BRCA2 on the other hand is a larger 3418 amino acid protein that acts as a scaffold for the DNA recombinase, RAD51. It contains eight BRC motifs that bind RAD51 and another distinct RAD51-binding domain at its carboxyl end. BRCA2 mediates RAD51 loading on to single-stranded DNA, a critical step in the homologous repair of double-stranded DNA. Figure courtesy Andrew Shuen, MD

**Table 6.2** Risks associated with BRCA2 mutations: non-breast/ovary sites by age of onset

Site	0–65 years of age	65–85 years of age	
	RR	95 % CI	RR 95 % CI
Buccal cavity + Pharynx	1.52	0.44–5.19	3.15 0.77–4.83
Stomach	2.57	1.13–5.84	1.93 0.77–4.83
Pancreas	5.54	2.72–11.32	1.61 0.45–5.72
Prostate	7.33	4.66–11.52	3.39 2.34–4.92
All except breast, ovary, prostate, pancreas	1.48	1.15–1.91	1.30 0.96–1.76

Breast Cancer Linkage Consortium, adapted from – Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst. 1999;91(15):1310–6

Particular mutations in *BRCA1* and *BRCA2* may confer higher RR of ovarian cancer than others, but currently this information is of limited clinical utility. Of course, men may transmit breast cancer susceptibility, but the mutation is usually non-penetrant for breast cancer in males. Among families with male breast cancer, 80 % are due to mutations in *BRCA2* and 20 % to *BRCA1*.

There is a high frequency of specific germline mutations in *BRCA1* and *BRCA2* in individuals of Ashkenazi Jewish origin (about 2 %; the *BRCA1* c.68\_69delAG (also known as 185delAG or 187delAG) and c.5266dupC *BRCA1* (also known as 5382insC) and c.5946delT *BRCA2* (also known as 6174delT) mutations), and up to 30 % of breast cancer cases in women from this ethnic group diagnosed with breast cancer under the age of 40 years, 40 % of breast cancer families, and 60 % of breast/ovarian families carry one of these germline mutations. A high frequency of specific *BRCA1/2* mutations has been found in other ethnic groups, probably due to a founder effect, for example, the 999del5 *BRCA2* mutation in Iceland, detected in 0.6 % of the population, 7.7 % of female breast cancer patients, and 40 % of males with breast cancer. In one study from Poland, recurrent mutations were found in 33 (94 %) of the 35 families with detected mutations. Three *BRCA1* mutations – c.5266dupC, c.181T>G, and 4153delA – accounted for 51, 20, and 11 % of the identified mutations, respectively (Gorski et al. 2000). Mutations in *BRCA2* were rare. These observations simplify *BRCA1/2* genetic testing for individuals of Polish origin. Many other populations are known to have founder mutations in one or other of these two genes (Fackenthal and Olopade 2007).

The proportion of breast cancer attributable to *BRCA1* mutations was estimated at 5.3 % in women diagnosed below the age of 40 years to 1 % in those diagnosed over the age of 70 years (Easton et al. 1995), and subsequent mutation analysis studies have proved these estimates to be approximately accurate (Whittemore et al. 2004b).

## BRCA Protein Function

*BRCA1* and *BRCA2* are large genes with no known homology, containing 22 and 26 exons, respectively (Fig. 6.3). Many, but not all of the functions of the *BRCA1* and *BRCA2* proteins revolve around facilitating the repair of double-strand DNA breaks.



In addition, BRCA1 has functions that are not related to DNA repair. These roles include cell checkpoint control, protein ubiquitination, and chromatin remodeling, and BRCA1 may also have a role as transcription factor (Narod and Foulkes 2004) (for excellent more recent reviews focusing on the nexus between genome integrity, DNA repair, and BRCA1, see Li and Greenberg 2012; Silver and Livingston 2012). Recent developments in the understanding of the function of BRCA1, discussed in the reviews cited above, include the potential differential effect of some RING-finger *BRCA1* mutations on E3 ubiquitin ligase activity (which may be important clinically, in that some mutations could have differing clinical effects) and the finding that BRCA1 knockout or depletion in mouse models resulted in a decrease in the number of pericentric heterochromatic foci. Their morphology was also altered. This study, focused on the connection between BRCA1 and heterochromatin, is supported by previous work on both BRCA1-related and basal-like (but BRCA1-intact) breast cancer where there seems to be loss of maintenance of silencing of the inactive X-chromosome (Ganesan et al. 2005). Both these studies point to a broader role for BRCA1 in tumor suppression. The critical enigma of why female *BRCA1* mutation carriers are so prone to develop breast and ovarian cancer remains unresolved. Several hypotheses have been proposed, for example, that there is of a restricted period of time during breast development when estrogen-driven proliferation can be influenced by the level of BRCA1 protein (Elledge and Amon 2002; Scully and Livingston 2000), that allele loss rates at BRCA1 differ between tissues (Monteiro 2003), that there is a role for BRCA1 in breast stem cell regulation (Foulkes 2004) and, now most recently, that the involvement of BRCA1 in removal of bulky adducts (e.g., UV photoproducts) might extend to the removal of the products of estrogen metabolism, in the form of DNA adducts (Pathania et al. 2011). Moreover, this function may be impaired in cells heterozygous for *BRCA1* mutations, and thus the specificity for breast cancer is related to dependency of this cancer on estrogen (Pathania et al. 2011).

Cells defective in BRCA1 or BRCA2 are hypersensitive to agents that cross-link DNA strands or that break double-stranded DNA, such as cisplatin and mitomycin C (Yuan et al. 1999; Moynahan et al. 2001; Tassone et al. 2003). In these cells, double-strand breaks are repaired in an error-prone fashion (e.g., via nonhomologous end joining), and errors can lead to chromosomal rearrangements (Patel et al. 1998; Zhong et al. 1999). Notably, BRCA1 and BRCA2 function in a common pathway that is responsible for the integrity of the genome and the maintenance of chromosomal stability (Venkitaraman 2002). In the last few years, this commonality has been exploited therapeutically by several groups. Studies of patients with triple-negative cancers receiving neo-adjuvant cisplatin-based chemotherapy showed that complete clinical responses were much more likely to occur among BRCA1 mutation carriers than noncarriers (Silver et al. 2010). Similar effects were seen in uncontrolled studies of breast cancer arising in *BRCA1* mutation carriers (Byrski et al. 2008). Taken together, these studies suggest that *BRCA1* (and possibly *BRCA2* mutation) carriers may receive greater benefit from platinating compounds than other women with cancer. Definitive studies are underway. Because breast and ovarian cancers in women heterozygous for mutations in *BRCA1* or *BRCA2* mutation



that carry a second somatic “hit” to *BRCA1* or *BRCA2* respectively will be rendered functionally null for the relevant protein and thus have impaired homologous DNA repair, PARP inhibitors (PARPi), which essentially convert single-strand breaks to double-strand breaks, were promoted as useful chemotherapeutic agents for breast and ovarian cancers in *BRCA1/2* carriers affected by cancer. An extended Phase I study (Fong et al. 2009) and two Phase II clinical trials in *BRCA1/2* carriers showed promise in the treatment of both metastatic breast (Tutt et al. 2010) and ovarian cancers (Audeh et al. 2010), but most “triple-negative” breast cancers do not respond to PARP inhibition (Gelmon et al. 2011). While the drugs are often initially effective in many mutation carriers, resistance often develops, by a number of different mechanisms, most notably revertant mutations that restore an open-reading frame resulting in the expression of a functional *BRCA1* or *BRCA2* protein (Swisher et al. 2008; Norquist et al. 2011; Edwards et al. 2008; Sakai et al. 2008). Perhaps because of such resistance, longer-term studies of PARP inhibitor treatment of ovarian cancer have not showed an improvement in overall survival (Ledermann et al. 2012).

As stated above, in the absence of underlying *BRCA1* or *BRCA2* mutations, most triple-negative breast cancers do not respond to PARPi, but a recent development suggests that PARPi-resistant triple-negative breast cancers might be converted to sensitivity to these drugs by the additions of PIK3CA inhibitors (Ibrahim et al. 2012; Pérez et al. 2012).

## Other Genes Involved in Breast Cancer Susceptibility

A number of studies have now tested for *BRCA1* and *BRCA2* mutations in population-based series of breast cancer cases, and thus the contribution of these two genes to familial aggregation can be assessed. Peto et al. (1999) identified 30 *BRCA1/2* mutations in 617 breast cancer patients diagnosed before age 46. Interestingly, only five of their mothers or sisters had had breast cancer, compared with 64 in the relatives of the 587 noncarriers. After allowing for the number of breast cancers that would be expected at population rates, and assuming a mutation sensitivity of 64 %, this would equate to approximately 16 % of the observed familial risk being due to *BRCA1* and *BRCA2*. In a previous linkage study, over 80 % of families with six or more cases of breast cancer were found to be linked to either *BRCA1* or *BRCA2*, but the proportion fell to 40 % in families with four or five cases, leaving room for other genes (Ford et al. 1998).

In the last few years, four genes have emerged as strong candidate breast cancer susceptibility genes – *CHEK2*, *BRIP1*, *ATM*, and *PALB2* (Foulkes 2008) – and the candidacy of other so-called “moderate-penetrance” breast cancer susceptibility genes (such as *RAD50* and *NBS1*) have been advanced. It is important to recognize that identified mutations in all these genes are either too low in frequency or of too low penetrance to account for more than a small part of the remaining familial cases. In particular, *BRIP1* appears to have a very limited role (Seal et al. 2006; Wong et al. 2011), but has recently been associated with ovarian carcinoma (see below). In families with a strong family history of breast cancer, these moderate-risk alleles could

be clinically useful (Byrnes et al. 2008). The same authors have suggested that the breast cancer penetrance for at least some *PALB2* alleles is as high as some *BRCA2* alleles (Erkko et al. 2008; Southey et al. 2010).

Approximately 50 % of women with Li–Fraumeni syndrome (see p. 271) develop breast cancer, particularly at young ages. The RR for breast cancer in women under 45 years of age in Li–Fraumeni syndrome families has been estimated at 17.9 (Garber et al. 1991). However, the proportion of cases of breast cancer overall is likely to be extremely small because fewer than 1 % of breast cancer cases can be demonstrated to have germline *TP53* mutations (Borresen et al. 1992), and even among early-onset breast cancer, *TP53* mutations have a minor role (Sidransky et al. 1992).

Other genes associated with a moderate to high penetrance for breast cancer include *PTEN* (Cowden Syndrome), *STK11* (Peutz–Jeghers syndrome), and *CDKN2A* (hereditary malignant melanoma). The contribution of mutations in all of these three genes to breast cancer incidence is negligible, but the risks for carriers can be as high as 50 %. Klinefelter syndrome (XXY) is also associated with an increased risk for breast cancer (p. 270).

Epidemiological data have demonstrated an increased RR of early-onset breast cancer in the female relatives of cases of ataxia telangiectasia (see p. 219), and the proportion of breast cancer due to heterozygosity for *ATM* mutations has been estimated to be 7 % overall, a smaller proportion at later ages at diagnosis than at earlier ages. Initial studies had suggested that a very small proportion of breast cancer cases, even in radiosensitive subjects, was attributable to mutations in this gene. One missense mutation, *ATM*\*7271T>G, has been associated with a high risk of breast cancer in a few families (Chenevix-Trench et al. 2002), but it is not frequently implicated in hereditary breast cancer (Szabo et al. 2004). The most comprehensive genetic epidemiological study suggested that the RR for breast cancer in *ATM* carriers is 2.2 (95 % CI 1.2–4.3), but is nearly 5 for those diagnosed under 40 years of age (Thompson et al. 2005). This study was supported by a definitive molecular study which identified deleterious mutations in 12 of 443 probands from UK familial breast cancer pedigrees and in 2 in 521 controls, leading to an estimated RR of 2.37 (95 % CI, 1.51–3.78) (Renwick et al. 2006), a number remarkably similar to the estimate from epidemiological studies. This study also emphasized the need for very large studies when looking at rare alleles with moderate risks. The previous negative studies listed above were underpowered to detect relative risks as low as 2.4. RR between 2.0 and 5.0 and have been termed moderate-risk alleles, whereas those below this are generally grouped together as low-risk alleles.

A rare novel type of mutation resulting in somatic mosaicism has been uncovered by next-generation sequencing. Truncating somatic mutations in *PPM1D* have been identified in small percentage of breast and ovarian cancers, but interestingly, they appear not to be heritable. They are only present in lymphocytes and not in the tumors occurring in those carrying these mutations. Also, they are not present in the offspring of carriers thus far tested and identifying *PPM1D* mutation carriers will be a challenge. The relative risk for breast and ovarian cancer, however, is substantial (likely >20) and would warrant preventive intervention (Ruark et al. 2013).

Several score of low-risk breast cancer susceptibility alleles have been discovered through powerful genome-wide association studies (GWAS) (Easton et al. 2007), and there are probably hundreds more such alleles, but currently their usefulness in the clinic is very limited. In the future, it is hoped that risk calculation programs, such as BOADICEA (Antoniou et al. 2004), and perhaps BRCAPRO, will be able to incorporate these genotypes into the risk model. If so, low-risk alleles could be of considerable interest in planning screening protocols (Pharoah et al. 2008). Until that time, lower-risk alleles are more relevant to the clinician as modifiers of high-penetrance alleles. For example, SNPs at *ESR1*, *TOX3*, and one on 2q (not in a gene) have been found to modify breast cancer risk in *BRCA1* carriers. By contrast, so far 11 SNPs modify risk in *BRCA2*-related breast cancer. This is probably related to the fact that more SNPs are known to modify ER-positive breast cancer than are known to modify ER-negative breast cancer. Several alleles also modify risk for ovarian cancer in *BRCA1* or *BRCA2* mutation carriers (Barnes and Antoniou 2012). Clearly, many more such loci will be identified, and perhaps this will be of clinical use in the next decade or so, but currently the effect sizes are not large enough to warrant altering clinical recommendations for mutation carriers.

## Histopathology of Breast Cancer and Its Relationship to Genetics

Breast cancers arising in *BRCA1* mutation carriers can often be distinguished from cancers occurring in *BRCA2* or non-*BRCA1/2* carriers on morphological (Lakhani et al. 1998), immunopathological (Lakhani et al. 2002), cytogenetic (Wessels et al. 2002), gene expression (Hedenfalk et al. 2001; Van't Veer et al. 2002; Sorlie et al. 2003), and mutational grounds (Nik-Zainal et al. 2012). *BRCA1*-related breast cancers are usually infiltrating ductal carcinomas of high grade. Although the term is seldom used now, studies have shown that an atypical medullary phenotype is more common in *BRCA1*-related breast cancer than in matched controls (Lakhani et al. 1998). *BRCA1*-related breast cancers are much more likely to be triple negative (TN) (ER, PR, and HER2 negative) than are other types of breast cancer (Schneider et al. 2008). Notably, some studies of *PALB2* mutation carriers have also noticed an excess of TN breast cancer, but comprehensive studies are required (Tischkowitz and Xia 2010). *BRCA2*-related cancers are usually ER positive, and unlike sporadic breast cancer, the percentage of tumors that are ER positive does not increase with age (Foulkes et al. 2004). It has been noted that HER2 positivity is commonly found in breast cancers arising in women with germline *TP53* mutations (Wilson et al. 2010; O'Shaughnessy et al. 2011), which could aid in selecting who to offer germline *TP53* testing.

Ductal carcinoma in situ (DCIS) and lobular carcinoma are underrepresented in *BRCA1* mutation carriers. Sequencing studies of women with DCIS have revealed a small percentage of *BRCA1* and *BRCA2* mutations (~1 and 2.5 %, respectively) (Claus et al. 2005).

## Genetic Counseling

Genetic counseling for women with a family history of breast cancer requires an initial assessment of their lifetime risk of developing breast cancer on the basis of empirical data derived from taking a family history that includes information about cancer type and age at onset in all first-degree and second-degree relatives and as many more distant relatives as possible. It is important to try and confirm diagnoses if it will make a material difference to the clinical decisions made. Risk estimates can be obtained using epidemiological data, or with the help of computer programs which calculate risks using these data, and can be expressed as a lifetime risk or as a risk for developing cancer over a shorter time period, such as the ensuing 10 years (Antoniou et al. 2004). Programs such as IBIS and BRCAPRO can also calculate the probability of being a *BRCA1/2* mutation carrier, although IBIS is limited to unaffected women. Hand-scoring, non-Bayesian methods, such as the Manchester scoring system have the benefit of simplicity and user-friendliness, relying on a scoring system for the numbers of affected relatives. They avoid the need for a computer program (Evans et al. 2004). Screening guidelines based on family history and genetic testing are available on the NICE website, <http://www.nice.org.uk/cg41>: “Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (partial update of CG14)”.

A woman whose mother has a germline breast cancer susceptibility mutation has a prior risk of 50 % of inheriting the susceptibility, so that her lifetime risk of developing breast cancer is about 40 % (assuming 80 % gene penetrance for breast cancer). However, if she remains healthy after the age of 50 years, her actual risk will have fallen because she has lived through a substantial amount of her risk period, with most hereditary breast cancer occurring at a younger age. The risk that the daughter of a gene carrier who remains unaffected at 50 years of age has inherited the susceptibility has fallen to approximately one-third, and if she remains healthy, it is less likely that she has inherited the susceptibility the older she becomes.

The probability that the family is segregating for a *BRCA1* or *BRCA2* germline mutation may be derived from family history data, in order to give an indication as to the likelihood that the consultant could be offered a predictive test for such a mutation. This chance is very dependent on age at diagnosis in the affected woman (there is a 17 % chance of a *BRCA1* mutation in breast cancer families with average age at diagnosis below 35 years, but a 1 % chance when the average age at diagnosis is over 59 years). A family history of ovarian cancer increases the chance of finding a *BRCA1* mutation, as does multiple primary breast or ovarian cancers in an affected woman of Ashkenazi Jewish origin (Couch et al. 1997).

The original model for counseling and genetic testing of women desiring and eligible for genetic testing includes a lengthy initial counseling, where the risks and benefits of genetic testing are fully discussed, with due attention being paid to all the implications of a positive or negative test result being discussed before testing, with offers of psychological support. Options for prophylactic and surveillance interventions should be discussed in detail before the test is undertaken, with additional discussions about insurance and employment issues. One of the

premises of this model is that many potential psychological sequelae of predictive testing exist, particularly in relation to psychiatric morbidity. Additionally, any effect on uptake of surveillance and prophylactic measures required careful consideration (van Oostrom et al. 2003). These procedures were put in place partly because the detection of a germline *BRCA1* or *BRCA2* mutation in an affected woman can be of great psychological impact and was considered by some to be possibly equivalent to the shock of the original cancer diagnosis. In addition, detailed counseling would need to cover the possibility of identifying a germline mutation of uncertain significance, especially in population groups that have not been extensively sampled.

This traditional model is the most common context in which women receive genetic testing. More recently, however, population-based testing of unaffected women without detailed counseling has been carried out (Metcalf et al. 2010). While long-term sequelae are not known, short-term data do not suggest harm (Metcalf et al. 2012). Clearly, testing before a cancer diagnosis is optimal if the “risks of knowledge” and negative effects of surgical intervention (e.g., preventive oophorectomy) are outweighed by the decrease in cancer incidence. It will not be possible to know this without long-term follow-up. Nevertheless, if the initial treatment of women with breast cancer could be significantly and positively influenced by knowledge of mutation status at the time of diagnosis, then the benefit of rapid, low-cost, tailored genetic testing may be greater than the risks of harm resulting from a more limited pretest counseling. Early studies involving full counseling have suggested that affected women who learn they are carriers at time of diagnosis or soon afterwards tend to make different surgical decisions than those who find out later (Schwartz et al. 2004, 2005); thus, there is at least precedent for considering testing at time of diagnosis.

## Screening and Prophylaxis

Screening for breast cancer is based upon the detection of early cancer and not of a premalignant lesion (Smith et al. 2000). Despite a meta-analysis that concluded that there is a reduction up to 18 % of the breast cancer mortality among 40–49 years old women following regular mammographic screening, the effectiveness of this tool for the surveillance of premenopausal women remains debatable. Indeed, after decades of research, the “mammography debate” continues with much vitriolic comment (Rogers 2003), and it seems unlikely that new data will help to resolve the issues easily (Goodman 2002).

The efficiency of screening should be higher if the women screened are at increased risk because of a family history of breast cancer, but as yearly mammography seems to be rather ineffective in *BRCA1/2* carriers (Brekelmans et al. 2001; Goffin et al. 2001; Tilanus-Linthorst et al. 2002), other screening modalities such as MRI have been found to be superior at detecting breast cancers.

Magnetic resonance imaging (MRI) is a non-ionizing imaging technique that has already been demonstrated to be sensitive for invasive breast cancer. Its sensitivity is less impaired than mammography by dense parenchyma. Preliminary results of a

German prospective nonrandomized pilot project (including 192 asymptomatic women proved or suspected to be *BRCA1/2* mutation carriers) demonstrated that the sensitivity and specificity of breast MRI was superior to conventional mammography and high-frequency breast ultrasound (Kuhl et al. 2000). Much larger studies in North America and Europe have confirmed that MRI is superior to mammography for the detection of breast cancers in *BRCA1/2* carriers (Kriege et al. 2004; Warner et al. 2004, 2011). It is not known if this will translate to a better long-term outcome but the data on medium-term survival are encouraging (Rijnsburger et al. 2010; Passaperuma et al. 2012). Interestingly, among those who develop an MRI-detected breast cancer, the survival for *BRCA1* mutation carriers may be inferior to *BRCA2* mutation carriers, and different screening regimens may be required for younger *BRCA* mutation carriers (Heijnsdijk et al. 2012).

For some women at very high risk of breast cancer (e.g., *BRCA1* or *BRCA2* mutation carriers, those with Cowden syndrome, Li–Fraumeni syndrome, or occasionally an undiagnosed dominant breast/ovarian cancer pedigree), preventive bilateral mastectomies may be the preferred option, but the women require careful counseling and a discussion of the residual risk of breast cancer following different types of surgical procedure (a subcutaneous mastectomy, leaving the nipple, may have a measurable residual risk, and a total mastectomy, with or without nipple-sparing, is probably the preferred option). Information is still accumulating about the efficacy of such prophylactic surgery, but so far, invasive breast cancers appear to be very rare after total mastectomy in *BRCA1/2* mutation carriers (Meijers-Heijboer et al. 2001; Rebbeck et al. 2004); by contrast, there are several reports of invasive breast cancer following subcutaneous mastectomy in *BRCA1* (Rebbeck et al. 2004) and *BRCA2* (Kasprzak et al. 2005) mutation carriers. Contralateral mastectomy should also be considered for women likely to be *BRCA1/2* mutation carriers who have had breast cancer because their risk of contralateral breast cancer is substantially increased to approximately 40 % at 10-year follow-up. Notably, the risk is reduced by tamoxifen and oophorectomy (Metcalf et al. 2004). Testing at time of breast cancer diagnosis is likely to increase the frequency of initial contralateral mastectomy (Schwartz et al. 2004).

At present, many screening protocols for *BRCA1/2* carriers include ovarian cancer surveillance, but the true value, if any, of regular assessment with CA-125 and transvaginal ultrasound is unknown, and both case reports (e.g., Hebert-Blouin et al. 2002) and recent biological data (Berns and Bowtell 2012), combined with modeling (Brown and Palmer 2009), suggest that these cancers arise very quickly and are probably not amenable to any currently available form of screening.

The role of chemoprophylaxis is still unclear in women with a family history of breast cancer, but drugs such as tamoxifen may be considered for such at-risk women; the data are conflicting, but point towards a benefit even for women who are destined to develop an ER-negative breast cancer. Although tamoxifen was rarely prescribed for this purpose by US oncologists (Robson 2002), it has now been recommended that either tamoxifen or raloxifene should be offered for 5 years to postmenopausal women with a uterus and at high risk of breast cancer, unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer, in the updated NICE guidelines, which also provide guidance on risk assessment and surveillance, at <http://www.nice.org.uk/CG164>.



Use of the oral contraceptive pill (OCP), even for relatively short periods, is protective against ovarian cancer in *BRCA1/2* mutation carriers (Narod et al. 1998). The situation for breast cancer risk is less clear. There have been four major studies. A large case-control study showed that early use, use before 1975, and prolonged use (>5 years) was associated with significantly increased risks of breast cancer among *BRCA1*, but not *BRCA2* mutation carriers (Narod et al. 2002). By contrast, a population-based study found no evidence for increased risk and even some suggestion of a decreased risk for *BRCA1* carriers (Milne et al. 2005). A third study found no excess risk for women diagnosed with breast cancer under 50 for women using the OCP for one year; for *BRCA2*, there was a slightly increased risk for women who used the OCP for more than 5 years (Haile et al. 2006). The most recent, a retrospective cohort study of 1,593 *BRCA1/2* mutation carriers, found an increased risk of breast cancer for *BRCA1/2* mutation carriers who ever used oral contraceptives (adjusted hazard ratio [HR]=1.47; 95 % CI, 1.16–1.87). HRs did not change when considering time since stopping use, age at start, or year of starting. Longer use was associated with an increased risk of breast cancer for both *BRCA1* and *BRCA2* mutation carriers, most notably among young women who used the OCP before their first full-term pregnancy (4 or more years of use before first full-term pregnancy was associated with a HR of 1.49 [95 % CI, 1.05–2.11] for *BRCA1* mutation carriers and HR=2.58 [95 % CI, 1.21–5.49] for *BRCA2* mutation carriers) (Brohet et al. 2007). Thus, there is no consensus between the four studies. Perhaps, until larger prospective studies are completed, it might be prudent to avoid OCP use in young *BRCA1/2* mutation carriers (i.e., less than 25 years old) who have not had a full-term pregnancy. On the other hand, a decision to pursue genetic testing prior to considering OCP use in a young woman at known genetic risk who is not otherwise inclined to learn of her mutation status would need to be carefully considered.

## Uterine Tumors

Tumors arising in the body of the uterus (for tumors of the uterine cervix, see later section) can arise from the endometrium or myometrium. The most common myometrial neoplasias are leiomyomas, while the most common endometrial tumors are endometrial carcinomas.

## Uterine Leiomyoma

Leiomyomas are benign, smooth muscle tumors with some connective tissue elements. They are very common, occurring in about 20 % of women over the age of 35 years, and the incidence increases with advancing age. They occur more frequently in women of Afro-Caribbean origin. Uterine leiomyomas are probably more common in first-degree relatives of index cases than in the general population. Uterine leiomyomas are component neoplasias of at least two heritable neoplasia syndromes: hereditary leiomyoma–renal cell carcinoma syndrome (HLRCC), which is also known as multiple cutaneous uterine leiomyomatosis (MCUL), and

Cowden syndrome. HLRCC/MCUL is caused by germline heterozygous mutations in the gene encoding fumarate hydratase (*FH*) (Alam et al. 2001; Tomlinson et al. 2002). *FH* is a nuclear gene encoding a mitochondrial enzyme involved in electron transport and the Krebs cycle (Eng et al. 2003). While germline heterozygous *FH* mutations cause HLRCC, germline homozygous mutations cause severe neurodegeneration (Eng et al. 2003). Although searching for germline *FH* mutations in women with isolated leiomyomas is not justified, *FH* sequencing should be offered in rare cases where familial uterine leiomyomatosis is present, even in the absence of other features associated with *FH* mutations (Tolvanen et al. 2012). Although few somatic intragenic mutations in *FH* have been found in sporadic uterine leiomyomas, biallelic inactivation by both genetic and nongenetic mechanisms occur with some frequency in these sporadic tumors (Kiuru et al. 2002; Lehtonen et al. 2004).

Uterine leiomyomas are common in the general population which makes it difficult to establish that they are true components of Cowden syndrome, but have been associated in some studies ([http://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_screening.pdf](http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf)). Uterine leiomyomas were reported in a woman carrying heterozygous mutations in both *PTEN* and *SDHC* (Zbuk et al. 2007).

## Carcinoma of the Uterus

This is the ninth most common malignancy in women with an incidence of 13 per 100,000 of population in the UK. In the USA, approximately 4 % of women will develop uterine cancer in a lifetime. The most common histological type is adenocarcinoma, and adenomatous hyperplasia (endometrial precancer, endometrial intraepithelial neoplasia) may be the premalignant lesion. Of all endometrial adenocarcinomas, the endometrioid histology is the most common. Squamous cell carcinomas, leiomyosarcomas, and mixed mesodermal tumors may occur, but are rare.

Epidemiological studies have shown a slight increase in RR for endometrial cancer in women with a family history of this cancer, leading to the conclusion that about 1 % of endometrial cancers may be explained by genetic factors. Endometrial adenocarcinoma is a component cancer of Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer syndrome) and of Cowden syndrome (p. 256). In one large French study that attempted to control for ascertainment bias, the risk to age 70 for endometrial carcinoma among *MLH1* mutation carriers was 54 % (95 % CI 20–80 %), for *MSH2* it was 21 % (8–77 %), and 16 % (8–32 %) for *MSH6*. While the point estimates are of definite value, the confidence intervals are too broad to be useful in the clinic. In contrast, a recent review of 113 families with *MSH6* mutations gave a much higher estimate of a 44 % risk of endometrial cancer in mutation carriers to 80 years age (95 % CI=30–58 %); and for any cancer associated with Lynch syndrome, and 47 % (95 % CI=32–66 %) for men and 40 % (95 % CI=32–52 %) and 65 % (95 % CI=53–78 %) for women. Compared with incidence for the general population, female mutation carriers had a 26-fold increased incidence of endometrial cancer (HR=25.5, 95 % CI=16.8–38.7) and a sixfold



increased incidence of other cancers associated with Lynch syndrome (HR=6.0, 95 % CI=3.4–10.7) (Baglietto et al 2010). This demonstrates some of the issues when comparing studies that focus on cancer-dense pedigrees, as often seen in the family cancer clinic, with those that are population based or that adjust for ascertainment bias in various ways.

In the French study, the risk of endometrial cancer by age 40 years for all three genes was two percent or lower, indicating that intensive early screening is probably not justified. In an international collaborative study, the 10-year cumulative risk of endometrial cancer for carriers of mismatch repair gene mutations (grouped together) who had not previously had cancer was approximately 10 % (95 % CI 3.5–26 %) (Win et al. 2012). In contrast, the same group reported that the 10-year cumulative risk of endometrial carcinoma was 23.4 % (95 % CI: 15–36 %) for women with mismatch repair gene mutations and a previous diagnosis of colorectal cancer. Roughly one-quarter of women diagnosed with a Lynch syndrome-associated colorectal cancer will develop endometrial cancer within 10 years of their diagnosis (Obermair et al. 2010). These findings should be taken into account when considering screening and preventive surgery options. Notably, there was no evidence that women with *MSH2* mutations were at higher risk of endometrial cancer than were female *MLH1* carriers, as previously suggested (Vasen et al. 2001). A retrospective study showed that prophylactic surgery is effective prevention for endometrial and ovarian cancer in MMR gene mutation carriers (Schmeler et al. 2006), but prospective studies have not been conducted. The risk of ovarian cancer was 3 % by age 50 in the French study (Bonadona et al. 2011) and was 3 % 10 years after identification of a MMR mutation in the Cancer Family Registry study (Win et al. 2012). Since the risk for *MLH1* and *MSH2* carriers in the French study increased rapidly after age 50 to reach 20–25 % by age 70, a strong case for peri- or postmenopausal hysterectomy with bilateral salpingo-oophorectomy can be made for MMR mutation gene carriers (NB fallopian tube cancer has been reported in Lynch syndrome patients) (Palma et al. 2008).

In terms of identifying Lynch syndrome in women with endometrial cancer, it has been pointed out that the difficulty in identifying MMR gene mutation carriers on clinical or morphological grounds justifies the use of immunohistochemistry for the four MMR proteins in all incident cases of endometrial cancers (Clarke and Cooper 2012). Nevertheless, it is clear that germline mutations would be found in a very small proportion of all such women tested.

Endometrioid endometrial carcinomas occur in women with Cowden syndrome, and a recent study estimated the lifetime risk for endometrial cancer to be 28 % (Tan et al. 2012), similar to the risk seen in *MSH2* mutation carriers. If confirmed, this would suggest preventive hysterectomy and enhanced surveillance might be indicated in *PTEN* mutation carriers. It is considered a major criterion for the clinical diagnosis of Cowden syndrome (p. 233) ([http://www.nccn.org/professionals/physician\\_gls/pdf/genetics\\_screening.pdf](http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf)).

Clinical surveillance for uterine malignancies in individuals at risk for endometrial cancers should be considered for all at-risk individuals. Indeed, the US-based National Comprehensive Cancer Network (NCCN) practice guidelines recommend

annual uterine surveillance by blind repeat biopsies of the endometrium from the age of 30 years for women with Lynch syndrome and from the age of 35–40 years for women with Cowden syndrome ([www.nccn.org](http://www.nccn.org)). After menopause, surveillance would change to annual endometrial (transabdominal or transvaginal) ultrasound with biopsy of suspicious lesions. These recommendations are similar to those put forward in 2006 by a group of European experts (Vasen et al. 2007), although since the value of surveillance is still unknown, the recommendation is that this should be offered to MMR mutation carriers from 35 to 40 years of age, preferably as part of a clinical trial (Vasen et al. 2013). Depending on their age, women who carry MMR gene mutations and have colorectal neoplasia should consider the option of concomitant prophylactic hysterectomy when they undergo bowel surgery for neoplasia.

## Choriocarcinoma

Choriocarcinomas can follow pregnancy of any type. Hydatidiform mole, the precursor choriocarcinomas, is thought to result from the fusion of two male gametes (without the participation of an ovum). Invasive moles, choriocarcinomas, occur with a frequency of 1 in 15,000 pregnancies in the USA; there is marked geographical variation, with a 10-fold higher incidence in Southeast Asia and the Far East. Familial biparental hydatidiform mole (FBHM) is the only recessive condition that is only expressed in females. Heterogeneity occurs; one locus was mapped to 19q13, and the responsible gene at this locus, *NLRP7*, was identified as the first gene that predisposed to choriocarcinomas (Murdoch et al. 2006). The protein is involved in the intracellular regulation of bacterial-induced inflammation and is a negative regulation interleukins. A second gene, *C6orf221* (*ECAT1*), was found to be mutated in three families with FBHM (Parry et al. 2011). The phenotypes of families with mutations in *ECAT1* and *NLRP7* appear to be indistinguishable.

## Fallopian Tube Carcinoma

This cancer was considered to be extremely rare, and in women not carrying *BRCA1/2* mutations, this is still the case. Over the last decade, however, increasingly persuasive data have been produced to suggest that a significant proportion of high-grade serous carcinomas (HGSC), apparently arising in the ovary, actually have arisen from the fallopian tube (Colgan et al. 2001; Crum et al. 2007; Crum et al. 2012; Piek et al. 2001; Piek et al. 2008). The risk for fallopian tube cancer per se is clearly increased in *BRCA1/2* mutation carriers (Zweemer et al. 2000; Rutter et al. 2003), and up to 40 % of women with fallopian tube cancer carry *BRCA1/2* mutations (Vicus et al. 2010). It has even been suggested that perhaps distal salpingectomy in both average and higher-risk women might be a way to prevent HGSC (Tone et al. 2012). Fallopian tube carcinoma has also been reported in Lynch

syndrome (Palma et al. 2008), but is very rare. In a recent next-generation sequencing study of 12 DNA repair-related cancer genes, of 31 patients with fallopian tube carcinoma, clearly deleterious mutations were seen in *BRCA1* in seven cases, in *BRCA2* in two cases, in *BARD1* in one case, and an unusual mosaic de novo missense mutation was seen in one case (Walsh et al. 2011). These findings suggest that exome sequencing, or panel-based screening for multiple genes, may soon replace the current labor-intensive and costly “gene-by-gene” approach (Table 6.3).

## Ovarian Cancer

Ovarian tumors may develop from germ, epithelial, or granulosa/theca cells. Germ cell tumors include dermoid cysts, teratomas, and gonadoblastomas. Sex cord-stromal tumors may develop from the mesenchyme, may include granulosa cell tumors, and may be hormone secreting. Benign serous and mucinous fibromas and cystadenomas are also seen. Most ovarian tumors are serous and mucinous adenocarcinomas. Carcinoma of the ovary is almost always derived from the epithelial cells and may originate more widely from coelomic epithelium (i.e., peritoneal carcinoma). Teratomas, embryonal carcinomas, sex cord–stromal tumors, choriocarcinoma, and dysgerminomas are much less common.

## Ovarian Carcinoma

The incidence of ovarian carcinoma is about 15 per 100,000 females in the UK; the lifetime risk to age 70 years is about 1.5 % in the UK and North America, slightly less in Southern Europe, making it the fifth most common malignancy in females in Western Europe and North America. Ovarian cancer has a very high mortality and is the most frequent cause of death from gynecological malignancies in the Western world. Worldwide, one of the highest incidence for ovarian cancer is seen in Israeli Jewish women who were born in North America or Europe – these are highly likely to be Ashkenazi Jews (13.5 per 100,000, cumulative incidence, 1.55 % to 74 years of age). Interestingly, in Israeli non-Jews, these figures are 3.0 per 100,000 and 0.32, respectively. These observations fit with the finding that up to 30 % of unselected Ashkenazi Jewish women with ovarian cancer carry mutations (Moslehi et al. 2000). This is a much higher figure than that observed in other groups. Early data suggested that for *BRCA1* in unselected non-Ashkenazi women with ovarian cancer, between 4 and 9 % can be expected to carry a *BRCA1* mutation, and between 0 and 4 % will carry *BRCA2* mutations, although this figure will be higher in certain founder populations, such as Iceland. The most recent data, using more comprehensive mutation analysis, has suggested that in population unselected for ethnicity, about 15 % of women with ovarian cancer carry a mutation in *BRCA1* (10 %) or *BRCA2* (5 %). Notably, about 50 % of *BRCA2* carriers are diagnosed at over 60 years of age, whereas 90 % of *BRCA1* carriers are diagnosed below 60 years’ age. Irrespective

**Table 6.3** Genetic disorders associated with ovarian neoplasms

Syndrome	Gene	Proportion of hereditary predisposition to OC (%)	Risk of OC by age 70 (%)	Other clinical features
Hereditary breast–ovarian cancer	<i>BRCA1</i>	60	20–50	Breast, fallopian tube, peritoneal, pancreatic cancer
Hereditary breast–ovarian cancer	<i>BRCA2</i>	25	10–30	Breast, prostate, pancreatic cancer, melanoma
RAD51C-related susceptibility to ovarian cancer	<i>RAD51C</i>	<1	≤10	Fanconi anemia-like condition in biallelic mutation carriers
RAD51D-related susceptibility to ovarian cancer	<i>RAD51D</i>	<1	≤10	None reported yet
BRIP1-related susceptibility to ovarian cancer	<i>BRIP1</i>	<1	≤10	Breast, pancreatic, and rectal ca (moderate risk)
HNPCC/Lynch syndrome	<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i>	10	≤10	Fanconi anemia in biallelic mutation carriers
Peutz–Jeghers Syndrome	<i>STK11</i>	<1 (ovarian sex cord–stromal tumors)	<5	Colon, endometrial, small bowel, urothelial, and pancreatic cancer
Cowden disease	<i>PTEN</i>	<1	<3	Mucocutaneous melanin spot, GI hamartomatous polyps, adenoma malignum of the uterine cervix, breast, GI, pancreatic cancer
Nevoid basal cell carcinoma (Gorlin syndrome)	<i>PTCH</i>	<1	<2	Multiple hamartomas, mucocutaneous signs, breast, thyroid cancer
DICER1-PPB multiple tumor syndrome	<i>DICER1</i>	<1 [ovarian sex cord–stromal (mainly) Sertoli–Leydig cell] tumor	<5	Basal cell/nevi carcinoma, palmar/plantar pits, skeletal abnormalities, odontogenic keratocysts, medulloblastoma
Multiple enchondromatosis (Ollier and Maffucci disease)	Somatic mosaic mutations in <i>IDH1</i> and <i>IDH2</i>	<1	<2	Pleuropulmonary blastoma, cystic nephroma, multinodular goiter, GI hamartomas, pituitary blastoma, other very rare manifestations
Epidermolytic palmoplantar keratoderma	<i>KRT9</i>	<1	<2	Osteochondromatosis, hemangiomas
				Epidermolytic hyperkeratosis

of family history, between 20 and 25 % of women diagnosed with ovarian cancer between the ages of 41 and 50 will carry a *BRCA1/2* mutation (Pal et al. 2005). These findings have important implications for referral guidelines to cancer genetics services. Among the Ashkenazim, these percentages are much higher, although some of the studies include selected cases. Overall, 25–30 % of all ovarian cancer in Ashkenazi Jewish women is attributable to one of the three founder mutations, with *BRCA1* mutation predominating at younger ages and *BRCA2* at older ages. Ovarian cancer is diagnosed at a significantly younger age in *BRCA1* carriers than in the general population. *BRCA2*-related ovarian cancers tend to be diagnosed at an older age than both the aforementioned groups.

Women with ovarian cancer (carcinoma) are more likely than expected to have a family history of ovarian neoplasia, and first-degree female relatives of patients with ovarian cancer are at increased risk. A collection of studies from around the world are summarized in Table 6.4; as can be seen, the odds ratios for ovarian cancer in association with a positive family history of ovarian cancer vary substantially, but are usually greater if the index case was diagnosed at a young age. The risk of death from ovarian cancer is very much greater if two first-degree relatives are affected. In this study, relatives of ovarian cancer cases also had significantly increased mortality from cancers of the stomach and rectum, but interestingly, the observed increased mortality from colon cancer, breast cancer, and pancreatic cancer failed to reach statistical significance.

Families in which there appears to be an autosomal, dominant susceptibility to ovarian cancer, with a high penetrance of the cancer in predisposed females have been recognized for years, and the identification of *BRCA1* and *BRCA2* has permitted more precise estimates of age-dependent cumulative incidence (i.e., penetrance). An analysis of 22 studies suggested that the risk of ovarian cancer among *BRCA1/2* carriers who were not selected on the basis of family history of breast or ovarian cancer is very low before age 40 (below 2 % for both genes), but rises substantially with age in the case of *BRCA1*, and is above 1 % per year from age 45 onwards, reaching 2.5 % per year by age 65. For *BRCA2*, the risks are lower, start to rise at later ages, and never reach 1 % per year (Antoniou et al. 2003).

The ovarian tumors arising in *BRCA1/2* carriers cases are carcinomas, with a predominance of serous papillary cystadenocarcinoma, and mucinous and borderline ovarian carcinoma are underrepresented.

The frequency of *BRCA* mutations in the general population is estimated to be about 1 in 800 for *BRCA1* and somewhat less for *BRCA2*, but it can vary significantly among some ethnic groups or geographic regions. Thus, the prevalence of the three *BRCA1/2* founder mutations among the Ashkenazim is approximately 1 in 50. The Icelandic population carries the founder *BRCA2* 999del5 mutation at a frequency of 0.4 %. The frequency of *BRCA1* and *BRCA2* mutations in unselected series of women with ovarian carcinoma has been extensively studied, particularly in the so-called founder populations. A founder effect can occur when a relatively small group is genetically isolated from the rest of the population, because of geographic conditions or religious belief. If an individual in that isolated population carries a rare genetic alteration, the frequency of this allele in the next generations

could increase in the absence of selection. Specific *BRCA1* and *BRCA2* mutations have been identified in diverse populations, such as in Ashkenazi Jewish, Icelandic, Swedish, Norwegian, Austrian, Dutch, British, Belgian, Russian, Hungarian, French Canadian, and Polish families (summarized in Fackenthal and Olopade 2007). The knowledge of well-characterized founder mutations in individuals of particular ethnic origins can simplify genetic counseling and testing, as the mutation screening can be limited to specific panels of mutations.

The founder mutations (often referred to as *BRCA1* 185delAG and 5382insC in *BRCA1*, *BRCA2* 6174delT) have been identified in the Ashkenazi Jewish families of Eastern European ancestry. These mutations are carried by about 2.5 % of the Ashkenazi Jewish population. These founder mutations are particularly common in Ashkenazi Jewish women with ovarian cancer, even without a family history of breast/ovarian cancer (Table 6.4).

These results show that among women with ovarian cancer, *BRCA1* and *BRCA2* mutations are at least 3 times more likely to be found in Ashkenazi Jewish women than in non-Ashkenazi women. Interestingly, among otherwise unselected, very young-onset cases (under 30 years of age at diagnosis) *BRCA1/2* mutations have not been observed, even though from epidemiological studies, mutations in genes are likely to be playing an important role in susceptibility.

There is evidence for genotype–phenotype relationships for ovarian cancer in *BRCA1/2* mutation carriers. Mutations in the 3' portion of the *BRCA1* gene (exons 13–24) were initially associated with a higher frequency of breast cancer relative to ovarian cancer in a series of 32 European families. This observation has not been confirmed by most larger studies (Stoppa-Lyonnet et al. 1997; Ford et al. 1998), although one study provided nonsignificant evidence in favor of the original finding (Moslehi et al. 2000). In a series of 25 English breast/ovarian cancer families, ovarian cancer was more prevalent than breast cancer when *BRCA2* truncating mutations were located in a region of approximately 3.3 kb in exon 11 (the ovarian cancer cluster region (OCCR), nucleotides 3035–6629). Additional data from 45 *BRCA2* families ascertained outside the UK provided support for this clustering. The analysis of 164 families with *BRCA2* mutations, 67 of whom had mutations in the OCCR, has been reported (Thompson and Easton 2001). The odds ratio for ovarian versus breast cancer in families with mutations in the OCCR, relative to non-OCCR mutations was 3.9 ( $P < 0.0001$ ), confirming the importance of the OCCR in terms of ovarian cancer risk, but the effect was lost when Ashkenazi Jewish cases were omitted (6174delT is an exon 11 mutation). Case reports of multiple-case ovarian cancer families with mutations outside the OCCR temper enthusiasm for the clinical utility of these observations (Al Saffar and Foulkes 2002).

The existence of a premalignant lesion for ovarian carcinoma is uncertain (Scully 2000). Careful histopathological analysis of prophylactic oophorectomy specimens among high-risk women, either because they have been identified as *BRCA1/2* mutation carriers or based on their family history, gave conflicting results regarding the presence of histological alterations that could evolve towards invasive carcinoma. A tiny carcinoma in situ was identified in an otherwise normal prophylactic oophorectomy specimen from a woman with a *BRCA1* mutation (Werness et al. 2000), but

**Table 6.4** Risk of ovarian cancer in women with a family history of OC: studies prior to *BRCA1/2* identification

Relatives studied	Country	Age group (years)	Cases	Controls	Odds ratio (95 % CI)	References
Any	USA	All	150	300	“No positive association”	Wynder et al. (1969)
First + second degree	USA	<50	150	150	15.7 (0.9–278)	Casagrande et al. (1979)
First degree	USA	45–74	62	1,068	18.2 (4.8–69)	Hildreth et al. (1981)
First degree	USA	18–80	215	215	11.3 (0.6–211)	Cramer et al. (1983)
First degree	Greece	All	146	243	$\infty$ (3.4– $\infty$ )	Tzonou et al. (1984)
First degree	Japan	N/A	110	220	$\infty$ (0.1– $\infty$ )	Mori et al. (1988)
First degree	USA	20–54	493	2,465	3.6 (1.8–7.1)	Schildkraut and Thompson (1988)
Second degree					2.9 (1.6–5.3)	
First degree	USA	20–79	296	343	3.3 (1.1–9.4)	Hartge et al. (1989)
First degree + aunts	Canada	All	197	210	2.5 (0.7–11.1)	Koch et al. (1989)
First degree	Italy	25–74	755	2,023	1.9 (1.1–3.6)	Parazzini et al. (1992)
First degree	USA	N/A	883	Population	2.1 (1.0–3.4)	Goldgar et al. (1994)
First degree	USA	<65	441	2,065	8.2 (3.0–23)	Rosenberg et al. (1994)
First degree	USA	All	662	2,647	4.3 (2.4–7.9)	Kerber and Slattery et al. (1995)

carcinoma in situ is very rarely seen in ovarian tissue, and this finding has not been replicated. Perhaps the tumor arose from ectopic fallopian tube epithelium that had been implanted in the ovary. More recently, attention has become focused on the hypothesis that the origin for clinically diagnosed *BRCA1/2*-related ovarian carcinoma is the distal fallopian tube (see section on fallopian tube carcinoma, page 104).

The incidence of primary serous carcinoma of the peritoneum among *BRCA1/2* carriers after oophorectomy is thought to be 0.2 % per year (Finch et al. 2006). The protective effect of oophorectomy against high-grade serous cancer in this study was approximately 80 %, which was in agreement with a population-based study from Israel (Rutter et al. 2003). These two studies suggested substantially less protection than was seen in selected series (Rebbeck et al. 2002), implying that among women who have undergone prophylactic surgery, this cancer may become one of the major threats to health among *BRCA1/2* mutation carriers in their later years. Peritoneal cancer is indistinguishable histologically or macroscopically from ovarian cancer



occurring among *BRCA1/2* mutation carriers and represents a major challenge in terms of prevention of cancer in mutation carriers. The potential increased risk of malignant transformation of the entire peritoneal surface is thought to reflect the common origin of the ovarian epithelium and peritoneum from embryonic mesoderm. However, the peritoneum on the surface of the ovary may be particularly vulnerable to malignant transformation as a result of repeated injury following ovulation and/or high levels of local estrogen exposure – or perhaps this leads to implantation of fimbrial epithelium that when internalized within the ovary, can undergo malignant change. Some peritoneal carcinomas may arise multifocally, particularly in the context of *BRCA1* mutations, and there may be a unique molecular pathogenesis of *BRCA1*-related papillary serous carcinoma of the peritoneum (Schorge et al. 2000). It seems implausible that these cancers arise from the fallopian tube.

The natural history of ovarian cancer in *BRCA* mutation carriers is thought to be different from sporadic ovarian cancer. Forty-three serous ovarian adenocarcinomas (81 % of the total) had an actuarial median survival of 77 months, compared with 29 months for the age, stage, and histological type-matched control group who were believed not to have mutations in *BRCA1* on the basis of family history ( $P < 0.001$ ). This good prognosis was attributed partly to the relative youth of the patients (mean age 48 years) but was also thought to be directly related to the presence of a *BRCA1* mutation. This study was criticized on methodological grounds, but a second study using a historical cohort approach gave similar results (Boyd et al. 2000). Furthermore, the better survival in hereditary cases was particularly noted for those women receiving platinum-containing chemotherapy. Other more recent studies have supported the notion that the prognosis is better for *BRCA1/2*-related ovarian cancer, but the durability of this survival advantage (most evident at 5 years following diagnosis) remains in question.

Mutations in other genes can cause ovarian cancer (Table 6.3). Lynch syndrome is one of the most common autosomal conditions predisposing to cancer, accounting for 3–4 % of all colorectal cancers (Moreira et al. 2012). Mutations in *MLH1* and *MSH2* are rare in ovarian cancers not selected on the basis of family history of cancer. The risk of developing ovarian cancer in MMR mutation carriers is about 8 %, with the highest risks in *MLH1* and *MSH2* mutation carriers and the lowest risk in *MSH6* mutation carriers (Walsh et al. 2011). Most symptomatic ovarian cancers (77–81 %) in Lynch syndrome are diagnosed at an early stage (FIGO stage I and II) and may have a relatively good prognosis (reviewed in Vasen et al. 2013). There may be an increased risk for ovarian cancer in Carney Complex (Stratakis et al. 2000), but the numbers are too small for accurate risk assessment.

A growing list of cancer predisposition alleles in the genes associated with the Fanconi anemia genetic pathway (Fanconi anemia-like) genes – *BRIP1* (Rafnar et al. 2011), *RAD51C* (Meindl et al. 2010), and *RAD51D* (Loveday et al. 2011) – have been shown to predispose to ovarian cancer. In addition, rare mutations in a number of genes involved in homologous repair, including *BARD1*, *CHEK1*, *MRE11A*, *NBN*, and *RAD50* have also been found in patients with ovarian cancer (Walsh et al. 2011).

Identifying patients with these mutations may have clinical importance because tumors with defects in the Fanconi anemia and homologous repair pathways are



sensitive to platinum agents and PARP inhibition. The therapeutic effectiveness of PARP inhibitors for treating ovarian cancer in women with germline *BRCA* mutations has been acclaimed, but more recent trials have failed to confirm an overall survival benefit with such treatment (Ledermann et al. 2012), possibly because of the development of resistance (Barber et al. 2013).

Prevention of hereditary ovarian cancer is a major topic and is beyond the scope of this book; suffice to say that medically, the oral contraceptive pill is likely to offer significant (40 % of more) risk reduction (Narod et al. 1998; Whittemore et al. 2004a). Surgically, ovarian removal (Rutter et al. 2003) is an option. Prophylactic salpingo-oophorectomy is often offered to women with germline *BRCA1* or *BRCA2* mutations, as the evidence is that it very much reduces the risk of ovarian cancer and also reduces the risk of breast cancer to 50 % in premenopausal women (Rutter et al. 2003; Domchek et al. 2010). It may also be offered to women with Lynch syndrome (Schmeler et al. 2006). While surgery clearly is effective in preventing serous papillary cancers arising from the ovary, the peritoneum remains at risk (as above).

The early detection of carcinoma at a stage in which it might be surgically curable, or more amenable to chemotherapeutic agents, would have a significant impact on prognosis. The traditional screening methods for ovarian carcinoma are the measurement of the serum tumor marker, CA-125, transvaginal ultrasonography, and clinical examination. None of these methods alone achieve the required level of sensitivity; for example, CA-125 detects only about two-thirds of Stage 1 ovarian tumors. In the general population, clinical examination, transabdominal, transvaginal (van Nagell et al. 2000) ultrasound, and serum CA-125 screening tests either alone or in combination have all been assessed as potential screening tests in various settings. However, no test or combination of tests has yet proved to be effective for population screening. In a longer-term follow-up of their previous study, Jacobs and colleagues showed that although the median survival in the screened group was significantly better than for the control group, the number of deaths from an index cancer did not differ significantly between the two groups, with 18 deaths in 10 977 controls versus 9 in 10 958 screened women, RR 2.0 (95 % CI 0.78–5.13) (Jacobs et al. 1999). Long-term follow-up of this study is awaited.

For women at high risk of ovarian carcinoma, it has been recommended that they have an annual pelvic examination, vaginal ultrasonography, and serum CA-125 measurement every 6- or 12-month intervals from their mid-20s or 5 years less than the earliest age of onset of ovarian cancer in the family. However, data showing clear benefit of such screening remains unconvincing. In the absence of good supportive evidence, it is appropriate to restrict these tests to a research setting. A worrying feature of hereditary ovarian cancer is the possibility that high-grade cancers can arise in very small foci that would not be detectable by ultrasound. A case report of a case of ultimately fatal advanced ovarian cancer diagnosed in a woman referred for a prophylactic oophorectomy was an early suggestion that delaying surgery could be dangerous (Rose and Hunter 1994). Studies among proven *BRCA1/2* carriers have supported this finding. Three of 33 women with *BRCA1/2* mutations were found to have early ovarian cancers lesions on examination of prophylactic oophorectomy specimens. Notably, two of the three cases were bilateral at diagnosis, and both were only noted on histopathological review and not in the operating room (Lu et al. 2000). Similarly, high-risk lesions or frank cancers can be found in the fallopian

tubes of *BRCA1/2* carriers at preventive oophorectomy (Leeper et al. 2002; Carcangiu et al. 2004; McEwen et al. 2004). In the latter study, 5 of 60 consecutive *BRCA1/2*-positive women undergoing preventive oophorectomy were found to have occult ovarian or fallopian cancer: one death had occurred at 4 years follow-up. In a similar study from the USA, 5 of 30 *BRCA1/2* carriers had cancer at surgery: one was a primary peritoneal cancer, three had tubal cancer, and one had ovarian adenofibroma with adjacent areas of low malignant potential carcinoma (Leeper et al. 2002). Taken together, these studies suggest that screening for ovarian cancer by ultrasound and CA-125 will prove to be insufficiently sensitive for routine use in *BRCA1/2* carriers, but definitive studies are awaited, and until such times as definitive benefit of screening has been demonstrated, it is appropriate to advocate consideration of prophylactic oophorectomy after childbearing age in high-risk women.

## Other Ovarian Neoplasms

Non-epithelial ovarian tumors are found with increased frequency in Peutz–Jeghers syndrome (sex cord-stromal and granulosa cell tumors which are often hormone secreting) and Gorlin syndrome (ovarian fibroma), and Ollier disease and Maffucci syndrome have both been associated with ovarian granulosa cell tumors with precocious pseudopuberty. A family has been described in which ovarian germ cell tumors were found in two daughters of a woman who herself had had an ovarian tumor in childhood, and her third child had a soft tissue sarcoma, but the paucity of such case reports of familial female germ cell tumors suggests that most sporadic forms of ovarian germ cell tumors are not attributable to inherited mutations in cancer susceptibility genes (Giambartolomei et al. 2009). Teratomas are thought to be pathogenic, arising from a single female germ cell after the first meiotic division.

There is a single-case report of a mixed ovarian germ cell tumor occurring in a *BRCA2* carrier – interestingly, no LOH was seen and thus it is possible that this was an unrelated, chance finding (Hamel et al. 2007). Ovarian fibromas have been reported in a family in which the condition could have been inherited as an autosomal sex-limited dominant trait. Ovarian sex cord–stromal tumors can occur in *STK11* mutation carrier (usually with annular tubules) and more recently have been associated with germline *DICER1* mutations, particularly in the form of Sertoli–Leydig cell tumors (SLCT), when there may be associated androgenization (Rio Frio et al. 2011; Slade et al. 2011). In this context, SLCTs can be associated with goiter (Rio Frio et al. 2011) or other features of the *DICER1*-PPB syndrome (Schultz et al. 2011). SLCTs have also occasionally reported in *STK11* mutation carriers (Hales et al. 1994; Howell et al. 2010).

Gonadoblastoma is a dysgenetic gonadoma that does not metastasize but which may be associated with dysgerminoma and other malignant germ cell elements. The overwhelming majority (96 %) of gonadoblastomas develop in dysgenetic gonads of 46XY individuals. Most patients with this tumor are phenotypic females, the rest are phenotypic males with abnormalities of the genitalia and undescended testes (Giambartolomei et al. 2009).

## Cancer of the Cervix

Carcinoma of the uterine cervix affects about 1 % of women, with an incidence of 8 and 12.5 per 100,000 population in Canada and the UK, respectively, but much higher incidence rates in some countries such as 67 per 100,000 in Zimbabwe and 34 per 100,000 in Columbia. It is strongly linked to human papillomavirus (HPV), indeed infection with this virus is almost always a requirement for squamous cell carcinoma of the cervix. The E6 and E7 viral proteins are consistently retained and expressed in these tumors and can be demonstrated to bind to the p53 and Rb protein products, respectively. The viral proteins may thus interfere with the normal tumor suppressor function of the cellular proteins. Host factors may also have a role in the pathogenesis of cervical carcinoma as women with HLA-DQw3 appear to be at increased risk of developing this tumor. Other HLA haplotypes have also been associated with increased risk (Apple et al. 1995).

There is a documented increased incidence of cervical cancer in women who were exposed to diethylstilboestrol in utero. Although cervical cancer may occur as a complication of the genetic skin conditions ectodermal dysplasia and dyskeratosis congenita, a genetic predisposition to this cancer is rare.

Family history studies of women with cervical cancer have not shown a striking excess of cervical cancer in female relatives, although some familial aggregation has been observed (Ahlbom et al. 1997; Magnusson et al. 2000; Horn et al. 2002), as might be expected, especially if the HLA data are taken into consideration. A substantial fraction of the familial factors appear to be nongenetic, but this may depend on the relationship studied: in the Magnusson study, shared environments explained concordance between sisters, but not between concordant mothers and daughters. Similarly, cigarette smoking-associated cancers (lung, larynx, lip, and cervix) were inter-associated in one systematic study (Goldgar et al. 1994). Nevertheless, the Breast Cancer Linkage Consortium did identify an excess of cervical cancer in *BRCA1* mutation carriers ( $RR = 3.72$ , 95 %  $CI < 2.26-6.10$ ,  $P < 0.001$ ) (Thompson and Easton 2002), but there have been no follow-up studies.

Screening for cervical cancer is offered as part of the population-screening program in the UK, and no particular addition to this has been suggested for women families with hereditary cancer syndromes, except Peutz–Jeghers syndrome, where adenoma malignum of the cervix can sometimes arise in females with Peutz–Jeghers syndrome who have developed sex cord ovarian tumors with annular tubules, resulting in hyperestrogenization (Beggs et al. 2010). It is etiologically distinct from squamous cell carcinoma. Primary melanoma of the cervix is very rare and does not seem to be related to mutations in *CDKN2A* or *BRCA2*.

Embryonal tumors of the cervix include embryonal rhabdomyosarcoma (cERMS) (McClellan et al. 2007) and primitive neuroectodermal tumors (Snijders-Keilholz et al. 2005); the latter have now been re-classified as Ewing tumors (Fletcher et al. 2002). Both types of cervical tumors are associated with germline *DICER1* mutations (Foulkes et al. 2011), and in the case of cERMS, somatic “second hits” in the RNase IIIb domain of *DICER1* have been identified (Heravi-Moussavi et al. 2012).

## Other Tumors of the Female Reproductive System

Cancer of the female genital organs other than of the uterus, cervix, and ovary has an incidence of about 3.6 per 100,000.

### Cancer of the External Genitalia

Cancer of the external genitalia is rare. Squamous cell carcinoma of the cervix and external genitalia may complicate dyskeratosis and congenital ectodermal dysplasia. Vulval carcinoma may complicate vulval lichen sclerosis (which can occur rarely as a familial condition, Vanin et al. 2002). Vulval neoplasia is generally “non-genetic” and is associated with HPV infection and smoking (Daling et al. 2002; Engelman et al. 2003). There is a possibility that genetic polymorphisms in genes altering susceptibility to cancer in smokers may also alter susceptibility to vulval and anal cancer. It can arise in Paget disease of the vulva and in Bowen disease of the vulva. Paget disease of the vulva is a rare intraepithelial cancer of the apocrine glands and is occasionally associated with an underlying adenocarcinoma (Tinari et al. 2002). Chromosomal 11p abnormalities have been described in the latter. Abnormalities of the *PRAD1* gene and *TP53* have been described in vulval carcinomas. Vulvar carcinoma occurs with increased frequency in Fanconi anemia (FA) and Morris syndrome. It appears that this increased prevalence in FA patients may be related to an increased susceptibility to HPV, and in FA patients an increased proportion of patients with FA and squamous cell carcinoma of the vulva are homozygous for Arg72, a p53 polymorphism that is thought to be associated with increased susceptibility to HPV infection (Kutler et al. 2003).

Primary malignant melanoma of the vulva is the second most common vulvar malignancy, an aggressive cancer, usually occurring on non-hairy skin, thus non-ultraviolet (UV) light associated (Ragnarsson-Olding 2004). A family history of cutaneous melanoma is found in 15 % of cases, and a germline mutation in the melanocortin type 1 receptor has been described in one case (Wechter et al. 2004).

### Vaginal Carcinoma

An increased occurrence of this squamous cell cancer is associated with maternal ingestion of diethylstilboestrol during pregnancy. Invasive epithelial and in situ vaginal cancers have many of the same risk factors as cervical cancer, including a strong relationship to HPV infection (Daling et al. 2002). A vaginal intraepithelial neoplasia has been reported in a carrier of a deleterious *PALB2* mutation (K.A. Schrader, personal communication).

Rare types of cancer of the vagina that have been reported are Brenner tumors and leiomyomas. The latter has been reported to occur as part of a dominantly

inherited syndrome of multiple adult-onset schwannomas, multiple nevi, and multiple vaginal leiomyomas. The nevi appear to be congenital in this condition. Giant hypertrophy of the labia minora and with neoplastic fibroblast and epithelial proliferation has been described in Ramon syndrome of arthritis, deafness, and pigmentary changes in the retina.

Primary vulval and vaginal extraosseous Ewing sarcoma and peripheral neuroectodermal tumor has been described (Vang et al. 2000).

## Prostate Cancer

Prostate cancer is the most common cancer and the second most common cause of cancer death in North American men. Population prostate cancer risk is approximately 0.5 % by the age of 65 years and 2 % by the age of 75 years. The etiology of prostate cancer is unknown, but androgen stimulation is implicated by observations of a low incidence in males castrated before the age of 40 years, and a high-fat diet has also been implicated. Evidence for a genetic contribution was provided by genetic epidemiological studies in Mormon families that suggested that the heritability of prostate cancer was greater than that of breast or colorectal cancer. A case-control study by Steinberg et al. (1990) found 15 % of prostate cancer patients had an affected father or brother, compared to 8 % of controls (Table 6.5).

Furthermore, the RR increased: (1) with the number of affected relatives such that men with one, two, and three affected first-degree relatives were at twofold, fivefold, and 11-fold increased risk for developing prostate cancer, respectively, and (2) the younger the age at onset of prostate cancer in the proband. Meikle and Smith (1990) reported. A 17-fold increase in RR of prostate cancer has been reported in brothers of men developing prostate cancer between 45 and 50 years of age. Segregation analysis of the family histories of 740 prostate cancer patients suggested that familial clustering of the disease could be caused by a rare, highly penetrant, dominantly inherited predisposition gene. Under the most likely genetic model, 43 % of early-onset prostate cancer (in men <55 years) would occur in gene carriers, but only 9 % of cases in men aged <85 years. This proposed model of a rare dominant predisposing gene (or genes) was similar to that suggested for breast cancer. Johns and Houlston (2003) undertook a meta-analysis of 13 studies of prostate cancer risk in first-degree relatives. They found that the pooled RR in first-degree relatives was 2.5 and 3.5 in men with one or two affected relatives. Risks were also increased if the affected relative had early-onset disease (<60 years). Nieder et al. (2003) provided cumulative risks by age according to family history details and ethnicity (i.e., Table 6.5). The clinical course of familial and sporadic prostate cancer appears to be similar, although the disease may be more aggressive in African-Americans.

Multiple prostate cancer susceptibility loci have been mapped by family linkage studies (e.g., *CAPB*, *HPC1*, *HPC2*, *HPX*, *MSR1*, *PCAP*, *HPC20*, *RNASEL*), but none of these equate with major high-penetrance susceptibility genes present in many populations (as for *BRCA1* and *BRCA2* in familial breast cancer). Although mutations in three candidate prostate cancer susceptibility genes have been reported,

**Table 6.5** Cumulative risks of prostate cancer according to ethnicity, age, and family history

Group	Cumulative risk of prostate cancer by age		
	50 years	60 years	70 years
White men			
No family history in (%)	0.2	2	7.5
One FDR in (%)	0.4	5.2	19
Two or more FDR in (%)	0.8	10	38
Black men			
No family history in (%)	0.4	3.6	10.6
One FDR in (%)	1.1	9.2	27.1
Two or more FDR in (%)	2.1	18	34

Adapted from Nieder et al. (2003)

FDR first-degree relative

*RNASEL* (*HPC1*, 1q24–q25), *MSR1* (8p22–p23), and *ELAC2* (*HPC2*, 17p11), in most cases these genes do not appear to represent rare highly penetrant loci and familial risks of prostate cancer may be explained better by a model of multiple interacting low-risk genetic variants. On the other hand, germline *BRCA2* mutations do account for a small but significant group (2–5 %) of familial prostate cancer clusters or early-onset cases (Edwards et al. 2002), and the relative risk of prostate cancer in carriers is increased significantly, higher at younger ages, in mutation carriers (RR 4.71) (Kirchhoff et al. 2004). The risk of prostate cancer is also increased in males with Lynch syndrome, highest in *MSH2* mutation carriers. Kaplan–Meier analysis suggested that cumulative risk by 70 years in MMR mutation carriers may be as high as 30 % (SE, 0.088) as compared to 8.0 % in the general population (Grindedal et al. 2009, see p. 262; Barrow et al. 2013).

The prognosis of prostate cancer in men with germline mutations in *BRCA2* appears to be worse than in the general population. Men who carry *BRCA2* mutations are more likely to develop early-onset prostate cancer (Grönberg et al. 2001; Willems et al. 2008; Tryggvadóttir et al. 2007; Mitra et al. 2008) and have a shorter survival time compared to *BRCA1* mutation carriers and to men in the general population (Narod et al. 2008; Edwards et al. 2010). In the latter study, the median survival in men with germline *BRCA2* mutation was 4.8 years, compared 8.5 years in controls ( $P=0.002$ ). Loss of heterozygosity was found in the majority of tumors of *BRCA2* mutation carriers and multivariate analysis confirmed that the poorer survival of prostate cancer in *BRCA2* mutation carriers is associated with the germline *BRCA2* mutation per se. Others have also suggested that the decreased survival in these men may be explained by the finding of an aggressive phenotype (Gleason score  $\geq 8$  and high T stage,  $\geq pT3$ ) in the majority of tumors in the *BRCA2* carriers who die from prostate cancer (Thorne et al. 2011a, b). A strikingly worse outcome for prostate cancer has been reported in carriers of founder *BRCA2* mutations in Icelandic population (Sigurdsson et al. 1997; Tryggvadóttir et al. 2007). In addition, the Ashkenazi Jewish *BRCA2* founder

mutation, c.5946delT (p. Ser1982fs), confers a 3-fold risk for prostate cancer, and carriers are more likely to develop high-grade prostate cancer than noncarrier (Gallagher et al. 2010).

Grönberg et al. (2001) reported a large family with a truncating *BRCA2* mutation which was responsible for hereditary prostate cancer in the father and four of his sons who developed early-onset disease. This mutation was also detected in three daughters diagnosed with breast cancer. All of the affected men with prostate cancer died of metastatic disease. Thus, more aggressive screening and treatment for prostate cancer may be justified, and an international study to this effect, known as IMPACT, is underway.

Fine-mapping by massively parallel sequencing of a previously identified susceptibility loci at 17q21–22 (Zuhlke et al. 2004) revealed a single mutation, *HOXB13* G84E, that co-segregated with the disease in four unrelated families and confirmed to be a risk allele in a large case–control population (Ewing et al. 2012). Independent analysis in an international sample of prostate cancer families validated G84E to be a disease-predisposing mutation, present among 5 % of prostate cancer families with an estimated odds ratio of 4.42 (Xu et al. 2013). Although in most Western populations the allele frequency is less than 1 per 1,000 men, the G84E variant has a much higher prevalence in Nordic populations and is found on a common haplotype block, suggesting presence of a founder effect originating in Finland; the missense variant appears to be very rare or absent among African-Americans and Asians (Gudmundsson et al. 2012). While it is unknown how the G84E variant predisposes to prostate cancer, the recurrent nature of the mutation and the lack of inactivating mutations suggest a gain-of-function mutation. Functional studies of the G84E variant are needed to clarify its role in cancer predisposition.

Men at increased risk of prostate cancer can be offered screening by annual measurement of prostate-specific antigen (PSA) and digital rectal examination from age 40 years. Male *BRCA1/BRCA2* mutation carriers are eligible for screening by annual PSA between 40 and 69 years with prostate biopsy if PSA > 3 mg/ml, under a research trial, IMPACT (Mitra et al. 2011).

Genome-wide association studies have discovered at least 50 separate loci that are associated with an increased risk for prostate cancer. All odds ratios are individually less than 1.5, but it is possible that combinations of alleles, and combining alleles with other established risk factors such as body mass index and family history could be of value in refining prostate cancer risk estimates. They could also be useful in modifying the risk of those carrying more highly penetrant alleles, such as *HOXB13* and *BRCA2* mutations.

## Testicular Neoplasms

Testicular cancer accounts for only 1 % of all malignancy in males (with an incidence of 4 per 100,000 males), but is the most frequent carcinoma in the 15–35-year age group. Most tumors are of germ cell origin (seminoma, teratoma) but some arise



from stromal cells (Sertoli cell), and gonadoblastoma contain germ cell and stromal elements.

Familial aggregation of testicular germ cell tumors accounts for up to 2 % of all adult cases. In a literature review, 24 father–son pairs, 45 pairs of non-twin brothers and 12 pairs of identical twins with testicular cancer were cited. Tumors are of the same histological type in 70 % of identical twin pairs, but were mostly of different histology in other degrees of relationship. Testicular tumors are bilateral in about 4 % of patients, which is suggestive of a genetic basis. In a Dutch single center study, RR of testicular cancer was increased 9- to 13-fold in brothers (Sonneveld et al. 1999). In an analysis of the Swedish Family-Cancer Database, familial risks were increased to 3.8-fold for fathers, 8.3-fold for brothers, and 3.9-fold for sons, and although seminomas showed a later age at onset than teratomas (30 versus 40 years), the familial risks were similar for the two tumor types (Dong et al. 2001). Forman et al. (1992) found that brothers of men with testicular cancer had a 2 % risk of developing testicular cancer by the age of 50 years, which corresponds to a 10-fold increase in RR. The mean age at diagnosis in familial cases was slightly younger than in sporadic cases (29.5 years versus 32.5 years).

Large families with a high incidence of testicular cancer have been described but are rare: Lynch and Walzak (1980) studied a large inbred Dutch kindred in which four individuals had histologically proven testicular cancers, and Goss and Bulbul (1990) reported a large cancer-prone family (including early-onset breast cancer) in which five males had testicular cancer. Nicholson and Harland (1995) and Heimdal et al. (1997) have suggested that familial clustering of testicular cancer might be attributable to a recessive gene. However, familial testicular cancer appears to be genetically heterogeneous, and an X-linked locus has been mapped (see below).

The principal risk factor for testicular cancer is cryptorchidism, which is associated with at least a 10-fold increase in risk, and orchidopexy should be performed in early childhood for boys with cryptorchidism if this risk is to be diminished. Genetic factors have been implicated in cryptorchidism because up to 14 % of cryptorchid males have an affected relative, but it is unclear to what extent this might explain the familial occurrence of testicular tumors. Patients with X-linked ichthyosis (steroid-sulfatase deficiency) appear to be at increased risk of cryptorchidism and testicular tumors. Testicular microcalcification is also a risk factor (Coffey et al. 2007).

Klinefelter syndrome has rarely been reported to predispose to testicular tumors, but in some cases this may be related to cryptorchidism. In one case, however, bilateral testicular teratoma occurred in a sib pair with Klinefelter syndrome. The risk of testicular cancer (seminoma, Sertoli cell, teratocarcinoma, and embryonal cell carcinoma) is unequivocally increased in patients with the testicular feminization syndrome, and prophylactic gonadectomy is usually performed after pubertal growth. Gonadoblastoma occurs in XY gonadal dysgenesis (see below), and also in patients with the WAGR syndrome (Wilms tumor–aniridia–genital abnormality–mental retardation, see p. 138). A subclass of Sertoli cell tumors (large cell calcifying) can be familial and can be associated with cardiac myxoma, endocrine activity, and pigmented skin lesions in Carney complex. Similar testicular lesions (intratubular



large cell hyalinizing Sertoli cell tumors) are also seen in Peutz–Jeghers syndrome (<http://www.uscap.org/site~/96th/SPECSURGH3v.htm>) where they often present with gynecomastia (Ulbright et al. 2007).

Chromosomal analysis of germ cell testicular tumors has implicated isochromosome of 12p as a specific finding. Although various associations between HLA haplotypes and testicular cancer have been proposed, HLA class I analysis of affected sib pairs provided no evidence of a HLA-linked testicular cancer susceptibility gene. However, Rapley et al. (2000) mapped a locus for testicular germ cell tumors (TGCT1) to Xq27 using families compatible with X inheritance. Cases linked to Xq27 were more likely to have undescended testis and bilateral disease. There was clear evidence of locus heterogeneity and autosomal susceptibility loci are likely.

More recent data suggests that no one single locus can account for a significant fraction of familial testicular tumors (Crockford et al. 2006). Interestingly, a Y-chromosome locus involved in infertility known as the “gr/gr” deletion is a rare, low-penetrance susceptibility allele for testicle tumors (particularly seminomas) with a population frequency of 0.013 and an odds ratio of 3.0 for seminoma ( $P=0.0004$ ). Genome-wide association studies have identified low-penetrance variants in six loci, implicating *KITLG*, *SPRY4*, and *BAK1* (all involved in the KIT/KITL pathway), *TERT* and *ATF7IP* (both involved in telomerase regulation), and *DMRT1* (involved in sex determination) in tumorigenesis (Kanetsky et al. 2009; Rapley et al. 2009; Turnbull et al. 2010). The six loci, together with the “gr/gr” deletion account for less than 15 % of the familial risk of TGCT, which implies that potentially many more risk alleles remain to be identified. The clinical utility of testing for these alleles is therefore currently limited.

The occurrence of testicular tumors in high-risk individuals can be prevented by appropriate measures. Cryptorchidism should be corrected early to avoid an increased risk of testicular tumors. Nonfunctioning testes that present a significant risk for tumorigenesis (as in the testicular feminization syndrome or intersex states) should be removed. Individuals thought to be at high risk of familial testicular tumors can be monitored by regular self-examination and ultrasonography.

## Testicular Tumors in Intersex States

Gonadoblastoma is a dysgenetic gonadoma that does not metastasize but which may be associated with dysgerminoma and other malignant germ cell elements. An overwhelming majority (96 %) of gonadoblastomas develop in dysgenetic gonads of 46XY individuals. Most patients with this tumor are phenotypic females, the rest are phenotypic males with abnormalities of the genitalia and undescended testes. The tumor is frequently bilateral, usually develops in the second decade, and may secrete estrogens or testosterone.

Germ cell tumors are rarely seen in individuals with gonadal dysgenesis who do not have any Y-chromosomal material present. Thus, girls with Turner syndrome

with the chromosomal constitution 45,X;45,X/46,XX;46,X,del(Xp) or 46,X,del(Xq) are not at an increased risk of this tumor, but in cases of gonadal dysgenesis due to chromosomal mosaicism such as 45,X/46,XY, or where a Y fragment is present, gonadoblastomas are a significant risk in the dysgenetic gonads, perhaps occurring in up to 20 % of cases. However, in a population-based study of girls with Turner syndrome, analyzed by PCR to detect Y-chromosome material, Gravholt et al. (2000) reported that although the frequency of Y-chromosome material is high in Turner syndrome (12.2 %), the occurrence of gonadoblastoma among Y-positive patients was less than in previous estimates (7–10 %). Gonadal extirpation has been suggested for such patients unless they have an almost normal male phenotype with scrotal testes. Nevertheless, careful follow-up (perhaps including testicular biopsy) is needed. The report of an infant girl with Turner syndrome, gonadoblastoma and 46XY(del Yp) karyotype indicated that the genes on the Y-chromosome that induce gonadoblastoma are distinct from the sex-determining locus, and detailed mapping of the Y-chromosome gonadoblastoma susceptibility region close to the centromere has been undertaken and candidate genes proposed (Lau 1999).

There is probably no increased risk of gonadoblastoma in Klinefelter syndrome (47, XXY) or in the XYY syndrome. However, gonadoblastoma is associated with sex reversal caused by 9p deletion (Livadas et al. 2003) and WAGR syndrome caused by 11p13 deletion (see p. 138).

Single gene defects can also cause gonadal dysgenesis, and gonadal tumors are found in at least 30 % of XY cases. The tumors are gonadoblastomas or dysgerminomas, which arise in the second or third decade. Autosomal recessive forms of XX gonadal dysgenesis are probably not associated with an increased risk for gonadoblastomas, but XY gonadal dysgenesis (Swyer syndrome), is frequently complicated by this tumor. Affected individuals are of normal stature and do not have the features of Turner syndrome, but have streak gonads. H-Y antigen may or may not be positive. It has been suggested that the risk of gonadoblastoma and dysgerminoma is confined to the H-Y antigen-positive cases. XY gonadal dysgenesis may also occur as an autosomal recessive condition, and gonadal tumors frequently complicate the familial testicular dysgenesis syndrome, one of this group of conditions. Again, H-Y antigen-positive cases appear to be the ones susceptible to gonadoblastomas, with a 55 % incidence. Gonadoblastoma may be associated with renal impairment and gonadal dysgenesis in Frasier syndrome (see p. 252).

The incidence of gonadal neoplasia in true hermaphrodites (individuals with both testicular and ovarian tissue) appears to be low, although both ovarian and testicular tumors have been reported. Complete testicular feminization (X-linked recessive inheritance) is associated with an increased risk of testicular malignancy (about 5 %), most commonly seminoma. If malignancy develops, it is usually after the age of 25 years, so that orchidectomy can be delayed until after pubertal feminization. The risk of neoplasia in incomplete androgen-insensitivity states, including Reifenstein syndrome, is considered to be low.

In the syndromes of persistent Mullerian duct and pseudovaginal perineoscrotal hypoplasia, the abnormally situated testes are susceptible to the development of seminomas, choriocarcinomas, embryonal carcinomas, gonadoblastomas, or

teratocarcinomas. The incidence of gonadal neoplasia may be slightly increased – to up to 4 % in 46XX cases and 10 % in 46XY cases.

In the conditions predisposing to gonadal tumors, it is advisable to remove the gonads prophylactically in the second decade.

## Epididymal Tumors

Benign epididymal cystadenomas occur in von Hippel–Lindau disease, when they are frequently bilateral. Although scrotal ultrasound scan can be useful for demonstrating sub-clinical involvement, the presence of epididymal cysts alone does not represent a reliable criterion for identifying gene carriers in von Hippel–Lindau disease families.

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## Chapter 7

# Urinary System

### Renal Neoplasms

Cancers of the kidney account for approximately 1.5 % of all cancers and cancer deaths (with an incidence of 5–8 per 100,000 population in the UK and commoner in males). Three main types of renal cancer are distinguished: (1) Wilms tumor, (2) renal cell carcinoma (RCC) (adenocarcinoma), and (3) medullary and transitional cell cancers of the renal pelvis.

#### *Wilms Tumor*

Wilms tumor is the most common solid tumor in children, with an incidence of approximately 10 per 100,000 live births and accounting for 8 % of all childhood cancers. Both sporadic and familial forms occur, although the latter is uncommon and only 1 % of Wilms tumor patients have a positive family history (Breslow et al. 1996). Median age at diagnosis of Wilms tumor is 3–4 years and 80 % of patients present by the age of 5 years. Approximately 5 % of cases have bilateral tumors. This subgroup has an earlier age at diagnosis (mean 30 months) and an increased incidence of renal blastemal rests and congenital abnormalities (Breslow and Beckwith 1982). In contrast to retinoblastoma, the age at onset and proportion of bilateral tumors are not significantly different in familial and sporadic cases. There are important associations between Wilms tumor and sporadic aniridia (see below), Beckwith–Wiedemann syndrome (p. 221), hemihypertrophy, genitourinary abnormalities (about 5 % of children with Wilms tumor have genitourinary abnormalities), Denys–Drash syndrome (p. 239), Frasier syndrome (p. 252), Perlman syndrome (p. 298), Simpson–Golabi syndrome (p. 306), and mosaic variegated aneuploidy. In addition, Wilms tumor has been associated occasionally with neurofibromatosis type 1, *BRCA1* mutations, and Bloom syndrome (Rahman et al. 1996). Familial Wilms tumor segregates as an autosomal dominant trait with incomplete penetrance.

Wilms tumor is thought to be derived from a mesenchymal renal stem cell or metanephric blastema. Islands of cells resembling metanephric blastema (nephrogenic rests) may persist into infancy and are found in 1 % of normal infant kidneys but in up to 40 % of kidneys with unilateral Wilms tumor and in almost 100 % of bilateral cases (Beckwith et al. 1990). Nephrogenic rests have been categorized into perilobar and intralobar rests. It appears that tumors associated with intralobar rests have an earlier age at onset and higher frequency of associated congenital abnormalities than those associated with perilobar rests.

### ***WAGR Syndrome (Wilms Tumour-Aniridia-Genital Abnormality-Mental Retardation) and the WT1 Gene***

Most children with WAGR syndrome have cytogenetically visible chromosome 11 deletions involving band 11p13 and the combination of aniridia with Wilms' tumor results from the deletion of the *WT1* (Wilms Tumor 1) and *PAX6* (aniridia) genes that are ~700 kb apart. Aniridia is fully penetrant, but Wilms' tumor occurs in only 50 % of cases. For patients with sporadic aniridia, the risk of Wilms' tumor is about 15 % (Muto et al. 2002), but molecular cytogenetic and genetic analysis can determine the extent of a deletion and hence the risk of Wilms' tumor (Clericuzio et al. 2011).

#### **WAGR Syndrome and the *WT1* Gene**

There is a high risk of Wilms tumor in isolated cases of aniridia, particularly when the patient also has genitourinary abnormalities and learning disability (mental retardation), the so-called Wilms tumor–aniridia–genital abnormality–mental retardation (WAGR) syndrome. This represents a contiguous gene syndrome. Up to 2 % of Wilms tumor patients have aniridia, compared to 2 per 100,000 of the general population. Wilms tumor is associated with sporadic aniridia and not with familial aniridia. For patients with sporadic aniridia, the risk of Wilms tumor had been estimated to be as high as 1 in 3, but this appears to be an overestimate and the risk may be closer to 15 % (Muto et al. 2002). The association of Wilms tumor with aniridia results from a contiguous deletion of the aniridia (*PAX6*) and Wilms tumor 1 (*WT1*) genes. Though many patients with Wilms tumor and aniridia have a cytogenetically visible chromosome 11p13 deletion, Wilms tumor can also occur in those with submicroscopic deletions that involve *PAX6* and *WT1* – indeed it has been reported that the risk of Wilms tumor is actually higher in those with submicroscopic deletions (van Heyningen et al. 2007). Molecular cytogenetic and genetic analysis can determine the extent of a deletion and hence the risk of Wilms' tumor (Clericuzio et al. 2011). Patients with intragenic *PAX6* mutations are not at risk of Wilms tumor, but only about 50 % of patients with *WT1* deletions develop Wilms tumor (Muto et al. 2002). Additional features of the WAGR complex include mental retardation,

ambiguous genitalia and gonadoblastoma, and, in some cases, obesity (Gul et al. 2002). There is a high incidence of bilateral tumors (36 %) and a younger age at diagnosis in children with Wilms tumor and aniridia compared to non-WAGR children. In addition, children with WAGR syndrome have a significant risk of renal failure, albeit it less than in Denys–Drash syndrome (38 and 62 %, respectively, at 20 years) (Breslow et al. 2000).

The *WT1* gene encodes a zinc-finger protein that is primarily expressed in renal blastemal cells during a critical period in the development of the glomerulus. The *WT1* gene product has a critical role in normal genitourinary development (see Denys–Drash syndrome [see p. 239]). Somatic *WT1* mutations occur in less than 10 % of sporadic Wilms tumors, and *WT1* mutations are rare in familial Wilms tumor. Pelletier et al. (1991) reported a father–son pair with Wilms tumor (and hypospadias and cryptorchidism in the son) associated with a germline *WT1* mutation. However, the associated genitourinary developmental abnormalities seen in *WT1* mutation carriers reduce the chances of familial transmission. Severe genital developmental abnormalities are seen in Denys–Drash syndrome, which is associated with dominant negative-acting *WT1* mutations (see p. 239).

A second Wilms tumor gene (*WT2*) was mapped by loss of heterozygosity studies to chromosome 11p15 in the region of the Beckwith–Wiedemann locus (see p. 221). Chromosome 11p15.5 allele loss preferentially affects the maternal allele that is compatible with a genomic imprinting effect and would be consistent with *WT2* being a maternally expressed imprinted tumor suppressor gene. The *CDKN1C* (*p57KIP2*) gene is a candidate imprinted tumor suppressor gene that is mutated or silenced in many patients with Beckwith–Wiedemann syndrome but is apparently not mutated in sporadic Wilms tumors. Loss of *IGF2* imprinting associated with *IGF2* overexpression occurs in a subset of Beckwith–Wiedemann syndrome patients (Lim and Maher 2010) and in the majority of sporadic Wilms tumors.

Rahman et al. (1996) mapped a familial Wilms tumor gene (*FWT1*) to chromosome 17q12–21. Kindreds linked to *FWT1* demonstrate a later age at onset than unlinked familial cases and sporadic cases and do not have developmental anomalies (Rahman et al. 1998). In addition there is evidence of incomplete penetrance (15–26 %) in *FWT1* kindreds suggesting that familial *WT1* may be underascertained (Rahman et al. 2000). A further familial Wilms tumor locus (*FWT2*) was mapped to 19q13.3–q13.4, but there is evidence for further locus heterogeneity (Huff et al. 1997; Rapley et al. 2000). Wilms tumor may also occur in children with biallelic *BRCA2* mutations (Fanconi anemia Type D1 see p. 249).

Cystic nephroma, a benign kidney tumor with differentiated septa but without blastemal elements, along with pleuropulmonary blastoma and ovarian Sertoli–Leydig cell tumors is associated with *DICER1* mutations (Hill et al. 2009). In addition, Wilms tumor has also been shown to be a component of the tumor spectrum associated with *DICER1* mutations (Foulkes et al. 2011).

All children at increased risk of Wilms tumor (e.g., with sporadic aniridia, hemihypertrophy, and Beckwith–Wiedemann syndrome) should be followed up carefully. A typical surveillance program would include 3-monthly renal ultrasound from birth to the age of 8 years. Nevertheless, Wilms tumor may develop



between ultrasound scans, and it has been suggested that parents should also be taught how to perform abdominal palpation. The exact risk threshold for offering Wilms tumor surveillance is not universally agreed. Scott et al. (2006a, b) suggested that screening should only be offered to those children with a 5 % or greater risk of developing Wilms' tumor and should only be offered to children with hemihypertrophy and paternal uniparental disomy 11p15 or isolated *H19* hypermethylation. In contrast, Clericuzio and Martin (2009) recommended that abdominal ultrasound screening should be offered to all children with idiopathic hemihypertrophy.

### ***Renal Cell Carcinoma (Adenocarcinoma, Hypernephroma)***

Renal cell carcinoma (RCC) accounts for almost 90 % of malignant renal tumors. Familial cases of RCC are infrequent and are estimated to account for about 3 % of all cases. McLaughlin et al. (1984), in a population-based case-control study, found a family history of RCC in 2.4 % of affected patients, compared to 1.4 % of controls. Sporadic RCC is histopathologically heterogeneous. The most common form is clear cell (conventional RCC) which accounts for 75–80 % of all cases. The most frequent non-clear cell histopathology is papillary RCC (~15 % of all cases) which can be divided into types 1 and 2. Chromophobe RCC and oncocytomas and other rare forms of RCC make up the remainder. In some cases, there is a good correlation between genetic causes of familial RCC and histopathological appearance. Thus, von Hippel–Lindau (VHL) disease (see p. 313) is the most frequent syndromic cause of renal carcinoma susceptibility, and RCC in VHL disease invariably has a clear cell appearance. Germline mutations in the *MET* proto-oncogene cause type 1 papillary RCC, while RCC in hereditary leiomyomatosis patients with germline fumarate hydratase mutations (see p. 201) is usually classified as type 2 papillary or collecting duct RCC. However, in Birt–Hogg–Dube syndrome although the characteristic tumor is that of a mixed chromophobe–oncocytoma appearance, other types of RCC, including clear cell, can occur (see p. 224). Similarly, the histological subtype of RCC associated with germline *SDHB* mutations is also variable (Maher 2010).

Familial RCC is characterized by (1) an early age at onset compared to sporadic cases, (2) frequent bilateralism, and (3) multicentricity. In addition, features of a susceptibility syndrome (e.g., VHL disease, hereditary leiomyomatosis and RCC syndrome or Birt–Hogg–Dube syndrome, germline succinate hydrogenase subunit gene mutation) may be present. Mean age at diagnosis in familial cases is about 45 years, more than 15 years earlier than for sporadic cases (Maher et al. 1990).

In addition to the major RCC susceptibility syndromes described above, familial clear cell RCC may be associated with constitutional translocations, characteristically but not exclusively, involving chromosome 3. The first such kindred was reported by Cohen et al. (1979) and contained ten affected patients in three generations. In this family, RCC segregated with a t(3:8)(p14.2;q24.1), and it was

estimated that each translocation carrier had an 87 % risk of developing this cancer by 60 years of age. Subsequently an increased risk of thyroid cancer was also reported in the family. At least 10 other chromosome 3 translocation-RCC families have been described, but the breakpoints and partner chromosome are heterogeneous. In the original t(3:8)(p14.2;q24.1) kindred, the 3p breakpoint occurred at the fragile site and disrupts the fragile histidine triad (*FHIT*) tumor suppressor gene. However, the precise role of *FHIT* (and the chromosome 8 gene *TRC8*) in RCC is unclear, and it has been suggested that instability of the translocated chromosome may be an important factor in this and other chromosome 3 translocation-RCC kindreds. All patients with possible RCC susceptibility should be examined for constitutional translocations. Adult translocation carriers in kindreds with chromosome 3 translocations and RCC should be offered regular renal surveillance (e.g., annual renal MRI or ultrasound scans). However, incidentally discovered chromosome 3 translocation carriers do not appear to require follow-up for RCC unless there is a personal or family history of RCC (or unless a translocation appears to disrupt a RCC suppressor gene) (Woodward et al. 2010).

Clinical and molecular genetic evidence of von Hippel–Lindau disease (see p. 313) should be sought in all cases of potential inherited clear cell RCC (e.g., familial, young onset, or multiple RCC).

Familial non-VHL clear cell RCC without evidence of a specific syndrome is generally characterized by autosomal dominant inheritance of susceptibility to RCC only (Teh et al. 1997; Woodward et al. 2000). It can be helpful to consider familial non-syndromic RCC according to the histopathology of the renal tumors (see above), e.g., the presence of type 1 papillary RCC would be an indication for *MET* gene analysis and non-clear cell RCC would exclude VHL disease. In a series of patients presenting with features suggestive of inherited non-syndromic RCC (mostly clear cell type), germline mutations in *SDHB* and *FLCN* (Birt–Hogg–Dube gene) were each detected in about 5 % of cases (Ricketts et al. 2008; Woodward et al. 2008). Hence, a preferred method for investigating potential inherited RCC is to test for mutations in a panel of inherited RCC genes (e.g., *VHL*, *FLCN*, *SDHB*, *SDHD*, *MET*, *FH*).

Renal tumors (consisting of a mixture of epithelial and stromal elements) may occur in hyperparathyroidism–jaw tumor syndrome (see p. 266) and rarely in tuberous sclerosis (although the most common renal tumor in this disease is angiomyolipoma) (see p. 307). Renal tumors may be seen in patients with Cowden syndrome or Cowden-like syndrome, particularly the subgroup in whom germline epimutations (promoter methylation of *KLLN* has been described) are found (see p. 233). Strategies for RCC are discussed in the sections on the relevant syndromes.

## Cancer of the Ureter and Renal Pelvis

Carcinoma of the renal pelvis accounts for approximately 10 % of all malignant renal tumors. Environmental causes of carcinoma of the renal pelvis include occupational exposure (as for bladder cancer) and prolonged excessive phenacetin ingestion.

Examples of familial ureteric and renal pelvis transitional cell carcinoma are rare. Lynch et al. (1979) described two families with a predisposition to carcinoma of the bladder and renal pelvis, and familial ureteric cancer (mother and son) was observed by Burkland and Juzek (1966). Cancer of the ureter and renal pelvis is a feature of hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome, see p. 256), and urothelial cancers may cluster in some HNPCC families. It has been suggested that the presence of an inverted growth pattern (endophytic) in urothelial carcinomas of the upper urinary tract may serve as a marker for identifying tumors with a higher frequency of microsatellite instability and thus help identify patients who should be offered testing for HNPCC (Hartmann et al. 2002).

Renal medullary carcinomas are very rare, highly aggressive tumors that occur in young patients with sickle cell trait or disease (Noguera-Irizarry et al. 2003).

## Bladder Cancer

Carcinoma of the bladder accounts for 4 % of all cancers (with an incidence in men of 30 per 100,000 and in women of 10 per 100,000 in the UK), is the fifth most common cancer in men, and has a peak prevalence in the seventh decade. Environmental factors, including tobacco, amine compounds used in the manufacture of dyes, and schistosomiasis, have been clearly implicated in bladder tumorigenesis, but genetic factors may also be relevant. Ninety percent of bladder tumors are transitional cell carcinomas, which may contain elements of squamous carcinoma or adenocarcinoma. Less commonly, sarcoma, melanoma, or small cell undifferentiated carcinoma may occur.

Familial clusters of bladder cancer were reported by Fraumeni and Thomas (1967) and McCullough et al. (1975). In these reports, bladder cancer affected a total of ten individuals from two-generation families. Lynch et al. (1979) also described two families showing a predisposition to transitional cell carcinoma of the bladder and renal pelvis. One individual developed bladder cancer at the age of 24 years. Familial clustering of bladder cancer could reflect shared exposure to environmental hazards or genetic susceptibility. A role for genetic factors is indicated by the association of bladder and other urothelial cancers with Lynch (HNPCC) syndrome and by the increased risk of bladder cancer in patients with germline *RBI* mutations. However, the most important contribution of genetic factors to bladder cancer risk is probably in determining individual susceptibility to environmental carcinogens, such as tobacco or occupational exposure to aromatic amine compounds. Hence, research into genetic susceptibility to bladder cancer has focused predominantly on the identification low-penetrance susceptibility genes, and large numbers of SNPs that convey small increases in relative risks have been identified. These SNPs are linked to genes implicated in detoxification of carcinogens, control of the cell cycle, and apoptosis and maintenance of DNA integrity (Golka et al. 2011).

Bladder tumors are frequently synchronous or metachronous. However, while these features are classical indicators of genetic susceptibility, molecular studies

have suggested that multicentricity does not reflect a high incidence of multiple primary tumors but rather that a single primary transformation event may seed other tumors by spread across the urothelium. Individuals who are at increased risk of bladder cancer should be screened by 6-monthly urinalysis and urinary cytology, with cystourethroscopy when these tests are abnormal. Analysis of urine sediment for microsatellite DNA markers may provide a novel method for monitoring bladder cancer recurrence (Steiner et al. 1997).

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## Chapter 8

# Blood and Lymph

### Leukemia

Leukemia is responsible for approximately 2 % of all cancers, with an incidence of about 8 per 100,000 in the UK. Acute myeloid and lymphoblastic leukemia (AML and ALL) account for about 1 % of all cancers and 1.5 % of cancer deaths. The age incidence of leukemia shows two peaks, in childhood and in the elderly. Genetic factors are not considered to have a prominent role in the pathogenesis of acute leukemia or in chronic myeloid leukemia, but have been implicated in chronic lymphocytic leukemia. Gunz et al. (1975) studied the incidence of leukemia in relatives of 909 patients with leukemia. The overall incidence of leukemia in first-degree relatives was three times higher than expected although only 2 % of patients had a first-degree relative with leukemia. Among the main subtypes of leukemia, an increased risk to relatives was most marked in chronic lymphocytic leukemia, less so in acute leukemia and absent in chronic myeloid leukemia. When familial clusters of leukemia have been reported, the type of leukemia in individual relatives is not always concordant. Familial leukemia does not necessarily indicate a genetic cause, and shared exposure to an environmental leukemogen also needs to be considered, particularly in childhood acute leukemia. In Western countries, leukemia affects approximately 1–2 % of the population. B cell chronic lymphocytic leukemia (CLL) is the most common form of leukemia, accounting for around 30 % of all cases. The incidence rate of CLL increases logarithmically from age 35, with a median age of diagnosis at 65 years. Acute myeloid and lymphoblastic leukemia (AML and ALL) account for about 1 % of all cancers and 1.5 % of cancer deaths. The age incidence of leukemia shows two peaks, in childhood and in the elderly. Genetic factors are not considered to have a prominent role in the pathogenesis of acute leukemia or chronic myeloid leukemia, but genes are being identified which do play a role in leukemia susceptibility, particularly chronic lymphocytic leukemia. Among the main subtypes of leukemia, an increased risk to relatives is most marked in chronic lymphocytic leukemia and less so in acute leukemia, but when familial clusters of leukemia have been reported, the type of leukemia in individual

**Table 8.1** Genetic disorders associated with leukemia

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Ataxia telangiectasia
Blackfan–Diamond syndrome
Bloom syndrome
Fanconi anemia
Biallelic mismatch repair gene mutations
Immune deficiency diseases (e.g., severe combined immunodeficiency, common variable immunodeficiency)
Incontinentia pigmenti
Kostmann syndrome
Li–Fraumeni syndrome
Lynch syndrome
N syndrome
Neurofibromatosis type 1
Seckel syndrome
Shwachman syndrome
Trisomy 21
Wiskott–Aldrich syndrome

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relatives is not always concordant. An increased relative risk of leukaemia is found in the siblings, especially twins, of cases of childhood ALL suggesting a significant contribution of genetic factors. Exposure to environmental factors may also play a part, particularly in childhood acute leukemia, where an infectious etiology has been suggested to account for increased numbers of cases in areas where there has been a sudden influx of people to a town with increased population mixing, a possible contributing cause for increased cases seen in areas around certain nuclear sites (Kinlen 2011; Bithell et al. 2008). Recent genome-wide association studies have identified loci which may contribute small alterations in relative risk of leukemia, especially CLL (Brown 2008).

Genetic disorders that have been associated with a predisposition to leukemia are shown in Table 8.1 and discussed in detail in Chap. 11. Genetic disorders are ought to account for only 3 % of childhood leukemia.

### ***Acute Lymphoblastic Leukemia (ALL)***

The most common malignancy in childhood, ALL accounts for 80 % of leukemia in the pediatric age group. ALL is less common in adults, in whom it constitutes approximately 15 % of acute leukemia. ALL is caused by the malignant proliferation of lymphoblasts which are the precursor cells of B and T lymphocytes. ALL is a heterogeneous disorder, and various criteria have been used for subclassification, for example, morphological (e.g., French–American–British classification), immunophenotyping (e.g., T cell, B cell, and various precursor B cell subtypes) or cytogenetic criteria (e.g., t(9;22), t(4;11), t(1;19), and t(12;21)). Immunological



classification can be refined by the molecular characterization of immunoglobulin heavy and light chain gene arrangements to define further the cell of origin of ALL.

Childhood leukemia is associated with genetic abnormalities in about 3 % and radiation exposure in less than 8 % of cases, so that the vast majority of cases are unexplained, although an infective (e.g., viral) origin has been postulated. Gunz et al. (1975) found that only 2 % of patients with acute leukemia had a first-degree relative with leukemia, and Till et al. (1975) observed that only 1.4 % of children with ALL had a close relative with leukemia or lymphoma. However, there is a significant risk of childhood leukemia in twins, particularly monozygotic. Thus Miller (1971) estimated that acute leukemia in an identical twin under 6 years of age is associated with a 1 in 6 risk that the co-twin will develop leukemia. The risk of leukemia in the unaffected twin is highest in infancy, decreases with age, and appears to be linked to a shared placental circulation. Thus, it is suggested that the leukemia lineage arises in utero in one twin and migrates to the other (Ford et al. 1993).

Familial clustering of adult ALL has been reported infrequently and might reflect shared environmental and/or genetic factors. De Moor et al. (1988) found 5 of 74 adult patients with ALL had a relative with acute leukemia or lymphoma and that this subgroup of patients with familial leukemia had a greater than expected incidence of HLA-Cw3 antigen. Horwitz et al. (1996) noted evidence of anticipation in familial leukemia, but for ALL this was based on only four pedigrees, each containing two affected individuals. In contrast to childhood ALL, twin-risks are not high in adult acute leukemia. Specific genetic disorders associated with ALL include Down syndrome, chromosome breakage syndromes (ataxia telangiectasia, Bloom syndrome), Li–Fraumeni syndrome, and immune deficiency disorders (severe combined, Bruton agammaglobulinemia, adenosine deaminase deficiency). Germ-line mutations in *PAX5* have recently been identified in familial pre-cell B-ALL (Shah et al. 2013).

### ***Acute Myeloid (Myelogenous) Leukemia***

Whereas ALL is the most common form of acute leukemia in children, AML predominates in adults. The overall incidence of AML is 2.5 cases/100,000 per year, with the highest incidence in those over the age of 60 years. Genetic disorders which have been associated with a predisposition to AML include Down syndrome, Fanconi anemia, neurofibromatosis type 1 (NF1), and Kostmann syndrome and DNA repair defects (see Chap. 11). An autosomal dominant syndrome of cerebellar ataxia, hypoplastic anemia, and predisposition to AML (associated with monosomy 7 in bone marrow cells) has been described (Daghistani et al. 1990). Bone marrow monosomy 7 is a frequent finding in chronic myeloproliferative disorders and AML, and only a small proportion of pediatric cases will have the ataxia pancytopenia syndrome. Monosomy 7 is the most common abnormality seen in familial

cases of AML, and familial clustering of AML with monosomy 7 may indeed occur (Kwong et al. 2000).

Inherited susceptibility to acute myeloid leukemia (AML) is rare apart from the conditions listed above (Horwitz et al. 1997). True nonsyndromic familial AML includes autosomal recessive disorders with myelodysplasia and monosomy 7, and some large pedigrees demonstrating autosomal dominant inheritance have been reported (Horwitz et al. 1996/1997). An autosomal dominant condition characterized by thrombocytopenia and platelet dense granule storage pool deficiency, platelet dysfunction, with a strong predisposition to acute myeloid leukemia and lymphoma, is well recognized, where the underlying genetic defect is a germline mutation in the *RUNX1* (runt-related transcription factor 1) (*AML1*, *CBFA2*) gene (Downton et al. 1985; Ganly et al. 2004). *RUNX1* was first identified as the gene on chromosome 21 that is rearranged in the somatic translocation t(8:21)(q22;q22.12) detected in patients with AML. The *RUNX1* protein complexes with the core-binding transcription factor (CBF) which regulates many genes involved in hematopoiesis. Other families have been described with familial AML associated with an inactivating germline *CEBPA* (CCAAT enhancer-binding protein) mutation, the gene encoding the granulocyte differentiating factor C/EBP $\alpha$ . There were latent periods of 10–30 years before the onset of overt leukemia in three affected patients in a family (Smith et al. 2004). Homozygous or monoallelic germline inactivating mutations in *EZH2* (a histone methyltransferase) have recently been found in about 12 % of a series of patients with myelodysplastic and myeloproliferative disorders (Ernst et al. 2011).

Davies et al. (2003) reported an increased risk of myeloid leukemia (40-fold), but not other cancers, in individuals with Prader–Willi syndrome.

Evidence of anticipation in familial AML has been noted such that of 79 individuals in nine families transmitting the disease, the mean age at onset in the grandparental generation was 57 years, compared to 32 years in the parental generation and 13 years in the youngest generation.

A rare form of AML, erythroleukemia (FAB-M6), may be familial (Di Guglielmo syndrome) in a minority of cases. Familial erythroleukemia is a leukemic or preleukemic state in which red cell proliferation is the predominant feature. Hematologic characteristics include ineffective and hyperplastic erythropoiesis with megaloblastic components accompanied by myeloblastic proliferation of varying degree (Park et al. 2002). A possible link between a missense mutation in the erythropoietin receptor (EPOR) and erythroleukemia has been reported (Le Couedic et al. 1996), but the role of the *EPOR* mutation in erythroleukemia is unclear.

## ***Chronic Myeloid Leukemia***

Chronic myeloid leukemia results from the malignant transformation of a pluripotent bone marrow stem cell. Typically, the disease has a triphasic course with an initial chronic phase (median duration 3.5 years) followed by an accelerated phase

and then, after 3–12 months, an acute blastic phase associated with a poor response to therapy. The hallmark of chronic myeloid leukemia is the Philadelphia chromosome (Ph), which was the first consistent chromosomal aberration to be associated with human malignancy (Nowell and Hungerford 1960). It is now recognized that the Ph chromosome is present in more than 90 % of patients with chronic myeloid leukemia and that a proportion of apparently Ph-negative chronic myeloid leukemia have a variant Ph translocation not visible by cytogenetic techniques (Kurzrock et al. 1988). The Ph chromosome is not specific for chronic myeloid leukemia, and it is also found (and is associated with a poor prognosis) in a small proportion of patients with ALL (20 % of adults, 5 % children) and AML (2 % of adults). The classic Ph<sub>3</sub> chromosome results from a translocation involving chromosomes 9 and 22, (t(9; 22)(q34; q11)). The breakpoint on chromosome 9 involves the Abelson oncogene (*ABL*), and on chromosome 22, the breakpoints occur within a small region that was originally designated the breakpoint cluster region (BCR). The BCR is a central segment within a 90-kb gene, now named the *BCR* gene (Laurent et al. 2001). The 9;22 translocation results in the juxtaposition of proximal 5' *BCR* gene exons (1, 2, and 3) and *ABL* sequences (exons 2–11, exons 1a and 1b).

Environmental agents associated with chronic myeloid leukemia include irradiation and chemical (e.g., benzene) exposure (Jacobs 1989), but there is relatively little evidence for a genetic predisposition. Familial chronic myeloid leukemia has been reported, and abnormal hematological investigations (evidence of a myeloproliferative disorder) have been observed in the healthy close relatives of cases. Nevertheless, familial cases of chronic myeloid leukemia appear to be rare.

## ***Chronic Lymphocytic Leukemia***

This is the most common form of leukemia accounting for >30 % of all cases and occurs particularly in the elderly, with a peak incidence between 60 and 80 years of age. Most cases are B cell type. This type of leukemia has the highest familial risk of all leukemias, with relatives of cases at significantly increased risk for CLL RR=7.52 (3.63–15.56), for non-Hodgkin lymphoma RR 1.45 (0.98–2.16), and Hodgkin lymphoma RR 2.35 (1.08–5.08) (Goldin et al. 2010; Yuille et al. 2000). Moreover, approximately 13 % of apparently healthy relatives of patients with familial CLL have a monoclonal blood B lymphocyte population detectable by cell flow analysis (3 % in controls).

In contrast to the acute leukemia and chronic myeloid leukemia, there is abundant evidence for a role of genetic factors in chronic lymphocytic leukemia. An association between disordered immune function and lymphoreticular malignancy is suggested by the finding that in some reports of familial chronic lymphocytic leukemia, autoimmune or immunological disorders have been noted among unaffected relatives. There is a fourfold excess of hematoproliferative malignancies among siblings of patients with chronic lymphocytic leukemia. Case-control studies have revealed relative risks in relatives ranging from 2.3 to 5.7 (reviewed by

Houlston et al. 2003). Among familial cases of chronic lymphocytic leukemia, the mean age at onset was >10 years earlier than in sporadic cases, and an increased risk of second primary tumors was noted (Ishibe et al. 2001). Among 18 affected individuals from seven pedigrees with dominantly inherited chronic lymphocytic leukemia, Horwitz et al. (1996) described evidence for anticipation in most cases, and this has been confirmed by others. The age at diagnosis in the offspring appears to be >20 years earlier than in affected parents.

Rawstron et al. (2002) detected subclinical levels of chronic lymphocytic leukemia-like cells in 14 % of relatives compared to about 1 % of normal controls suggesting that although the lifetime risk of chronic lymphocytic leukemia in familial cases is 20–30 %, there may be a significant incidence of subclinical disease.

The relative risks of lymphoproliferative disease in first-degree relatives of CLL cases have been found to be 1.8 for B cell NHL, 2.2 for indolent B cell NHL, 1.6 for follicular lymphoma, 3.3 for hairy cell leukemia, and 4 % for LPL/Waldenstroms macroglobulinemia (Goldin et al. 2010).

Rare high-penetrance and more common lower-penetrance susceptibility alleles are thought to be implicated in familial chronic lymphocytic leukemia. Recent genome-wide association studies have found several low-penetrance risk alleles for CLL (DiBernardo et al. 2008; Crowther-Swanepoel et al. 2010) and ALL each conferring small relative risks of disease (1.2–1.7 per allele), which act independently, such that the 2 % of the population who carry 13 or more risk alleles would have an eightfold increased risk of disease. Interestingly, these variants are involved in lymphoid cell development (Houlston 2010).

Germline mutations in *DAPK1*, a Ca<sup>2+</sup>/calmodulin-dependent serine/threonine kinase that acts as a positive regulator of apoptosis in part via phosphorylation of *p53* causing loss or reduced expression of *DAPK1*, cause an inherited susceptibility to CLL (Lynch et al. 2002, 2008b; Raval et al. 2007). *DAPK1* expression of the CLL allele may be downregulated due to increased HOXB7 binding, and promotor methylation results in additional loss of *DAPK1* expression.

Somatic inactivation of the ataxia-telangiectasia gene (*ATM*, see p. 219) occurs in >20 % of chronic lymphocytic leukemia cases, and in some cases, a germline mutation is also present. However while heterozygous *ATM* mutations may confer an increased risk of chronic lymphocytic leukemia, it seems likely that germline *ATM* mutations do not make a major contribution to familial cases of chronic lymphocytic leukemia (Houlston et al. 2003). Wiley et al. (2002) reported that a loss-of-function polymorphism in the cytolytic P2X7 receptor gene was overrepresented in patients with chronic lymphocytic leukemia compared to controls. However in another study, the P2X7 SNP was associated with survival in, but not risk of chronic lymphocytic leukemia (Thunberg et al. 2002).

Familial clustering (sibling or parent–child pairs) of hairy cell leukemia, an uncommon subtype of chronic lymphocytic leukemia with a prevalence of 1 per 150,000, has been reported in at least 30 cases (Colovic et al. 2001; Cetiner et al. 2003). Linkage to specific HLA haplotype has been suggested, but the influence of genetic and environmental factors in familial cases is unclear.

The first-degree relative of an affected person may have an eightfold increased risk of developing CLL themselves, and a 2.6 relative risk of any other lymphoproliferative disorder, but considering the population risk of these conditions is low, the absolute risk is low, and early detection of CLL is not likely to affect outcome, therefore surveillance would not be recommended.

Other subtypes of leukemia which may occur commonly in certain genetic conditions include juvenile myelomonocytic leukemia (JMML), where about 10 % of cases arise in children with neurofibromatosis type 1 (NF1), and in Noonan syndrome (see p. 297), a condition due to germline gain of function mutations in one of the oncogenes in the RAS signaling pathway, including *PTPN11*, *SOS1*, *RAF1*, *KRAS* and *CBL* (Pandit et al. 2007). Children with Noonan syndrome (NS) are at increased risk of developing juvenile myelomonocytic leukemia or a myeloproliferative disorder associated with NS (MPD/NS) resembling JMML in the first weeks of life. JMML constitutes about 30 % of childhood cases of myelodysplastic syndrome and 2 % of leukemia. Whereas JMML is an aggressive disorder requiring hematopoietic stem cell transplantation, MPD/NS may resolve without treatment, and cases with spontaneous remission have also been reported (Bastida et al. 2011).

CBL is an E3 ubiquitin protein ligase responsible for the inactivation of protein tyrosine kinases by tagging them for degradation. Somatic mutations in this gene, as with *PTPN11*, *KRAS*, and *NRAS*, are well characterized in a variety of leukemia, particularly Juvenile myelomonocytic leukemia (JMML) and CML. Germline mutations in the *CBL* gene have been identified in a very small proportion of Noonan syndrome patients with a predisposition to JMML (Niemeyer et al. 2010). These children have impaired growth, developmental delay, and cryptorchidism.

Legius syndrome, due to germline mutations in the *SPRED1* gene, is a syndrome characterized by café-au-lait macules, axillary and inguinal freckling, and neurofibromas and schwannomas. There is an increased risk of JMML in this condition also.

In Down syndrome, there is a 500-fold increased risk of acute megakaryoblastic leukemia, with an overall risk of developing leukemia of about 2 %, and about 10 % of DS patients have transient myeloproliferative disorder (TMD) at birth. TMD is the clonal proliferation of myeloid blasts, usually with megakaryoblastic features and presents almost exclusively in DS patients (Klusmann et al. 2007; Izraeli et al. 2007). The symptoms vary from asymptomatic leukocytosis to severe disease causing multiorgan failure. The disorder regresses in about 80 % cases, but about 20 % of cases will develop AML, usually by 5 years of age (Rabin and Whitlock 2009). TMD is a preleukemic state, and additional mutations of genes regulating the proliferation of the megakaryocyte progenitors such as *GATA-1* and *RUNX-1* need to occur for disease progression (Izraeli 2005). *GATA1* mutations are almost universally found in the AML of children with DS, and these may arise very early in the child's life.

Children with DS are also predisposed to ALL but much less so than to acute megakaryocytic leukemia. Twenty to thirty-three percent of DS ALL cases are found to have a point mutation in exon 14 of *JAK2*, compared to 0 out of 41 *JAK2* mutations

in non-DS ALL patients (Kearney et al. 2009). Patients with a *JAK2* mutation usually present earlier and with a higher WBC count than other ALL patients (Tigay 2009). *JAK2* mutations confer a cell advantage by promoting cell growth via the JAK/STAT signaling pathway (Mulligan 2008), and the mutations found in DS patients appear to be specific for DS ALL (Bercovich et al. 2008; Rabin and Whitlock 2009).

In non-DS patients, the most common genetic association seen in ALL is the *TEL-AML1* translocation between chromosomes 12 and 21, which accounts for about 25 % of childhood ALL (Armstrong and Look 2005). The mechanism by which the fusion protein formed by this translocation causes leukemogenesis is unclear, but the roles of both *TEL* and *AML1* have been shown to be vital in hematopoiesis. The translocation disrupts parts of *AML1* known as the core-binding factor, causing disruption of normal differentiation of B cell progenitors (Ford et al. 2009). The translocation can be found in the blood cells of patients at birth, which is many years before the age at which ALL patients typically present, as it takes so many years for the disease to develop sufficiently to present clinically (Armstrong and Look 2005).

## ***Polycythemia***

Increased red cell mass may be a primary abnormality, as in polycythemia rubra vera, or secondary to a variety of causes including hypoxia, renal cysts or tumors, and genetic disorders (benign primary familial polycythemia or familial erythrocytosis), such as inherited hemoglobin variants (e.g., hemoglobin Chesapeake), familial disorders of erythropoietin regulation (Kralovics et al. 1998), and recessive von Hippel–Lindau (*VHL*) gene mutations as in Chuvash polycythemia (Ang et al. 2002). However, there is evidence for further loci for autosomal dominant primary familial polycythemia (Jedlickova et al. 2003).

Polycythemia rubra vera is an uncommon myeloproliferative disorder (five new cases/million per year) in which increased red cell mass is usually associated with increased white cell and platelet counts. Polycythemia rubra vera usually pursues a chronic course, but there is a significant risk of an acute leukemic transformation occurring. Clonal cytogenetic abnormalities, such as del(20q), trisomy 8 and 9, del(13q), and dupl(1q), have been reported in a minority of patients with polycythemia rubra vera but are present in most patients with leukemic transformation (Heim and Mitelman 1987). More than 95 % of individuals with polycythemia vera and 50–60 % of individuals with essential thrombocythemia have an acquired activating point mutation in the cytoplasmic tyrosine kinase gene *JAK2*, *V617F*, which appears to be the underlying somatic mutation leading to clonal expansion of myeloid progenitor cells. In the remaining cases, there may be other mutations in the *JAK2* gene. Somatic mutations in the *TET2* gene have also been found in cases of polycythemia vera. Familial polycythemia rubra vera is rare, but the relative risk of the disorder in first-degree relatives of index cases is three to fourfold in individuals carrying the same haplotype block including the 3' portion of *JAK2* (Campbell 2009). This must be distinguished from the more common benign familial polycythemia which is not associated with leukemia. Inheritance of this appears to be autosomal dominant with incomplete inheritance (Kralovics et al. 2003).

*MPL* mutations may be detected in patients with myeloproliferative disorders without demonstrable mutations in *JAK2* (Ma et al. 2011).

Trisomy 8 and 9, del(13q) and dupl(1q), have been reported in a minority of patients with polycythemia rubra vera but are present in most patients with leukemic transformation (Heim and Mitelman 1987). More than 95 % of individuals with polycythemia vera and 50–60 % of individuals with essential thrombocythemia have an acquired activating point mutation in the cytoplasmic tyrosine kinase gene *JAK2*, V617F, which appears to be the underlying somatic mutation leading to clonal expansion of myeloid progenitor cells. In the remaining cases there may be other mutations in the *JAK2* gene, familial polycythemia rubra vera is rare, but the relative risk of the disorder in first-degree relatives of index cases is three to fourfold in individuals carrying the same haplotype block including the 3' portion of *JAK2* (reviewed by Campbell 2009). This must be distinguished from the more common benign familial polycythemia which is not associated with leukemia.

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*MPL* mutations may be detected in patients with Myelofroliferative disorders without demonstrable mutations in *JAK2* (Ma et al. 2011).

## ***Thrombocythemia***

Primary or essential thrombocythemia is a myeloproliferative disorder characterized by megakaryocyte hyperplasia and elevated platelet count. The main complications are bleeding and thrombotic events, and occasionally, acute leukemic transformation can occur. Familial essential thrombocythemia has been reported. Familial cases may be inherited as an autosomal dominant trait and may be caused by mutations in the thrombopoietin gene (*THPO*) on chromosome 3, or its receptor c-Mpl on chromosome 1p34 (Ding et al. 2004; Kondo et al. 1998). Large families with multiple generations involved (and male-to-male transmission in some cases) have been described (Schlemper et al. 1994; Kikuchi et al. 1995, van Dijken et al. 1996). Activating mutations in the *MPL* gene, which encodes the receptor for the major hormone driving platelet production, may be seen in 5 % of patients with thrombocythemia, and 50–60 % cases have a somatic point mutation in *JAK2* (Scott et al. 2007). Somatic mutations in the *TET2*, *ASXL1*, and *SH2B3* genes have also been found.

## **Lymphoma**

The two major categories of malignant lymphoma are Hodgkin disease (which accounts for just under half of the total) and non-Hodgkin lymphoma. The latter is a heterogeneous group of disorders, most are of monoclonal B cell origin, and a lesser number are of T cell or non-T non-B type. Genetic disorders that predispose to malignant lymphoma are listed in Table 8.2 and discussed in Chap. 11. Clearly,



**Table 8.2** Genetic disorders predisposing to lymphoma

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Ataxia telangiectasia
Chediak–Higashi syndrome
Common variable immunodeficiency
HyerIgM syndrome
Hypogammaglobulinemia
Severe combined immunodeficiency
Wiskott–Aldrich syndrome
X-linked lymphoproliferative disease

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there is a strong association between genetic disorders that cause clinical immunodeficiency and the development of malignant lymphoma. Furthermore, the incidence of lymphoproliferative disorders is increased among patients with immunodeficiency secondary to therapeutic immunosuppression or human immunodeficiency virus (HIV) infection. Although many lymphomas in immune-deficient individuals are of B cell origin, some are derived from other cells such as T lymphocytes (Baumler et al. 2003).

Tumors, especially lymphoproliferative disorders, are the second leading cause of death in immunodeficiency disorders, and it is estimated that 15–25 % of patients with the three major immunodeficiency syndromes (Wiskott–Aldrich syndrome, AT and common variable immunodeficiency) develop cancer. Approximately 60 % of cancers reported in patients with immunodeficiency disorders are lymphomas, and non-Hodgkin lymphoma is about six times as frequent as Hodgkin disease in these patients.

There is a slight increase in risk of lymphoma in the relatives of patients with hemopoietic malignancy (Chang et al. 2005; Altieri et al. 2006).

In patients with childhood onset of colonic adenocarcinoma, lymphoma, and brain tumors, (Menko et al. 2004; Poley et al. 2007) homozygous germline mutations in the *MSH6* gene have been identified, and in other patients, biallelic germline mutations in other genes involved in repair of microsatellite errors in DNA have been detected. Leukemia is thus a feature of the homozygous state for germline mutations in the “MMR” genes, which in heterozygous individuals cause Lynch syndrome (constitutional mismatch repair deficiency, p. 232).

A subset of patients with lymphoma have been found to have germline mutations in the perforin gene. Patients with biallelic mutations in this gene may have familial hemophagocytic lymphohistiocytosis (HLH), but a few such patients have been found to have Hodgkin or non-Hodgkin lymphoma. (Clementi et al. 2005).

## ***Hodgkin Disease***

This has an incidence of 2–3 per 100,000 population in the UK. Analysis of the age at onset of Hodgkin disease reveals a bimodal distribution, with one peak around the age of 25 years, then decreasing to a plateau in middle age, after which rates increase with advancing age for the second peak. The disease is more common in males than in females, in people of higher socioeconomic status, and in smaller families. The

etiology of Hodgkin disease is unknown, but an infective agent has been suggested, particularly in the younger age group and in the nodular sclerosis subtype. An association between familial clustering of multiple sclerosis and young-adult-onset Hodgkin lymphoma (HL) has been reported and suggests that the two conditions share environmental and/or constitutional factors (Hjalgrim et al. 2004; Shugart et al. 2000).

Ferraris et al. (1997) reviewed the literature on familial Hodgkin disease. They confirmed an excess of males in familial cases, that the male-to-female ratio (1.5:1) was similar in familial and sporadic cases, and that the age distribution of familial cases shows a single major peak between 15 and 34 years of age. Both genetic and environmental (e.g., viral infections) factors have been implicated in familial clustering of Hodgkin disease. Analysis of 432 sets of twins affected by Hodgkin disease revealed that 0 of 187 dizygotic twins were concordant for Hodgkin disease, compared to 10 of 179 monozygotic twins – expected cases  $>0.1$  for each group (Mack et al. 1995). The higher concordance in monozygotic twins compared to dizygotic twins clearly implicates genetic factors in familial clustering of Hodgkin disease in young adults. In a study of Hodgkin disease in Sweden, Shugart et al. (2000) estimated the heritability to be 28 % and suggested that there was significant evidence for anticipation in parent–child pairs with Hodgkin disease (mean difference 14 years). The relative risk of HL in relatives of cases is about 3.1, and there is also an increased relative risk for chronic lymphatic leukemia and non-Hodgkin lymphoma, and these relative risks are higher in relatives of young-onset cases (Goldin et al. 2004).

Epidemiological evidence suggests that Hodgkin disease may be a rare outcome of a specific infective agent, possibly Epstein–Barr virus (EBV). However EBV infection is common and often asymptomatic suggesting that additional factors, such as inherited immune response variants, might be implicated in susceptibility to Hodgkin disease. Hence a number of groups have investigated the associations between Hodgkin disease and HLA loci. Linkage studies in multiple-case families have confirmed an association with a susceptibility gene at the HLA locus and are consistent with a recessive gene which would account for a twofold increase in relative risk for siblings of patients with Hodgkin disease (Chakravarti et al. 1986). Linkage to the HLA class II region has also been demonstrated (Klitz et al. 1994); in particular, alleles at the HLA-DPB1 locus have been implicated specific histological subtypes, and an association with EBV-positive cases has been suggested (Taylor et al. 1999; Alexander et al. 2001). A recent assessment suggests that HLA A determinants contribute additively with one or more other genes to susceptibility to Hodgkin's (Shugart and Collins 2000). There is an increased incidence of Hodgkin disease in immunodeficient patients, and it accounts for about 10 % of tumors associated with primary immunodeficiency disorders. The mean age at diagnosis of Hodgkin disease in immunodeficient patients is 10.9 years, although there was a wide range, from less than 1–73 years (Kersey et al. 1988). Compared to pediatric patients with Hodgkin disease and no immunodeficiency disorder, there is an excess of mixed cellularity and lymphocyte depletion subtypes. However, most lymphomas that occur in immunodeficient individuals are categorized as non-Hodgkin lymphoma. The recent finding of chromosomal rearrangements involving *JAK2*, t(4;9)(q21;p24) *JAK2* rearrangements, including the novel *SEC31A-JAK2*

fusion, which are recurrent in classical Hodgkin lymphoma, is of importance; the t(4;9)(q21;p24) leads to a novel *SEC31A-JAK2* fusion which is oncogenic in vitro and acts as a constitutively activated tyrosine kinase that is sensitive to JAK inhibitors (Van Roosbroeck et al. 2011).

Germline mutations in *NPAT* (nuclear protein ataxia-telangiectasia locus) have been found to segregate with nodular lymphocyte predominant Hodgkin's lymphoma in a family and have also been detected in sporadic cases of the disease, suggesting that these mutations confer an increased risk (OR = 4.11) of this condition (Saarinen et al. 2011a, b).

## ***Non-Hodgkin Lymphoma***

This is a heterogeneous group of disorders with a wide range of histological, immunological, and cytogenetic subtypes. Non-Hodgkin lymphoma is the most frequent tumor to complicate the primary immunodeficiency syndromes (see Table 8.2) and may also occur in families of patients with chronic lymphocytic leukemia.

The most frequent causes of non-Hodgkin lymphoma complicating primary immunodeficiency are ataxia telangiectasia, Wiskott–Aldrich syndrome, common variable immunodeficiency, and severe combined immunodeficiency (see Chap. 11. Kersey et al. 1988), and it is the predominant malignancy in each of these disorders. Mean age at diagnosis is 7 years (from range less than 1–75 years), and the brain and gastrointestinal tract are frequent presenting sites. Compared to non-Hodgkin lymphoma in non-immunodeficient patients, lymph node involvement is less common. Most non-Hodgkin lymphoma in primary immunodeficient children is of B cell origin, but the lymphomas in ataxia telangiectasia are very heterogeneous, with all the major histological sub-groups represented. There appears to be no relationship between the severity of immunodeficiency and the risk of malignancy (Kersey et al. 1988).

A tendency for familial aggregations of hematolymphoproliferative cancers is recognized. Pottern et al. (1991) found 4.5 % of patients with non-Hodgkin lymphoma had at least one sibling and 3.3 % had a parent with a hematoproliferative cancer, while only 1.7 % of controls had an affected sibling and 2.2 % had a parent with a hematoproliferative cancer. There is a fourfold excess of leukemia and lymphomas among first-degree relatives of patients with non-Hodgkin lymphoma. When familial aggregations of hematoproliferative cancers occur, there is often no particular pattern of tumor type, so that although concordant cancers may occur, so may seemingly diverse cell types. A history of hemopoietic malignancy in any first-degree relative has been found to be associated with an increased risk of all non-Hodgkin's lymphoma (OR = 1.8), more pronounced in siblings than in parent–child relationships (Chang et al. 2005). Familial clustering of lymphoma is uncommon, but Lynch et al. (1989) reported a single exceptional family with seven cases of malignant lymphoma (six non-Hodgkin lymphoma and one Hodgkin lymphoma) in three generations with autosomal dominant inheritance. However

most family clusters are small. In familial clusters of non-Hodgkin lymphoma with vertical transmission, evidence for anticipation has been reported (Wiernik et al. 2000; Shugart et al. 2001).

Wiernik et al. (2000) analyzed 11 published reports of multigenerational familial non-Hodgkin lymphoma (NHL) and 18 previously unreported families with familial NHL for evidence of anticipation. The median age of onset in the child and parent generations of all families (48.5 and 78.3 years, respectively) and in the selected pairs (52.5 and 71.5 years, respectively) was significantly different. A significant difference was observed between the ages of onset between the child generation and that of the SEER population but not between the parent generation and the SEER population. They thus concluded that anticipation in familial NHL is a genuine phenomenon.

Using the Swedish Family-Cancer Database, Altieri et al. (2005) calculated standardized incidence ratios (SIRs) for histopathology-specific subtypes of NHL in 4,455 offspring with NHL whose parents or sibs were affected with different types of lymphoproliferative malignancies. SIRs for affected patients with a parental history of NHL were significantly increased for NHL (1.8) and diffuse large B cell lymphoma (2.3). SIRs for affected patients with a sib history of NHL were significantly increased for NHL (1.9), follicular lymphoma (2.3), and B cell lymphoma not otherwise specified (3.4). With a parental history of histopathology-specific concordant cancer, familial risks were significantly increased for diffuse large B cell lymphoma, follicular NHL, plasma cell myeloma, and chronic lymphocytic leukemia (SIRs of 11.8, 6.1, 2.5, and 5.9, respectively).

Clementi et al. (2005) reported 4 patients with non-Hodgkin lymphoma with features of hemophagocytic lymphohistiocytosis who had mutations in the perforin gene.

Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma, accounting for 30–40 % of cases. Survival of the malignant cells is dependent on constitutive activation of the nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling pathway. In normal B cells, antigen receptor-induced NF- $\kappa$ B activation requires CARD11, a cytoplasmic scaffolding protein. Missense mutations in *CARD11* have been demonstrated in about 10 % of LBCL biopsies, all within exons encoding the coiled-coil domain. Such experimental *CARD11* mutants cause constitutive NF- $\kappa$ B activation and enhanced NF- $\kappa$ B activity upon antigen receptor stimulation (Lenz et al. 2008; Davis et al. 2010).

Follicular lymphoma susceptibility has been associated with a SNP on chromosome 6p21.33 (Skibola et al. 2009).

## Myeloma

Reports of sibling pairs with multiple myeloma (MM) suggest that occasionally, genetic factors may predispose to myeloma, and Hemminki (2002) reported that offspring of multiple myeloma cases had a fourfold increased risk of disease. Horwitz et al. (1985) reviewed 30 families with two affected siblings and a further nine families with three affected siblings. In two reports of twins with multiple myeloma (Judson

et al. 1985; Comotti et al. 1987), one emphasized the contribution of shared environment and the other genetic factors. A 2 % incidence of plasma cell disorders in siblings of myeloma patients has been reported, but this may not be excessive (Horwitz et al. 1985). There have been a few families described with several cases of MM, although these are rare (Lynch et al. 2008b). Lynch et al. (2001) described a large kindred with familial multiple myeloma in three cases and a monoclonal gammopathy of unknown significance in two further relatives. Although there is no case for routine screening of relatives of myeloma patients, when familial myeloma is found, first-degree relatives should be screened (by blood and urine electrophoresis) and those with benign monoclonal gammopathy kept under surveillance. There is evidence for an increased relative risk of multiple myeloma in relatives of MM cases (SIR 2.45), chronic lymphatic leukemia (2.45), and non-Hodgkin lymphoma (1.34) (Altieri et al. 2005). A hereditary predisposition to B cell proliferative diseases has been established, and IgG/A and IgM disorders may occur together in families, where enhanced B cell responsiveness may be found in healthy subjects clustered around cases (Steingrimsdottir et al. 2011).

## Waldenstrom Macroglobulinemia

Familial occurrences of Waldenstrom macroglobulinemia, a rare subtype of non-Hodgkin lymphoma, are uncommon but well described (Renier et al. 1989; Blattner et al. 1980). It has been suggested that 4 % of relatives of affected persons have a monoclonal IgM component (Kalfs and Hijmans 1969). In the family of Blattner et al. (1980), all four affected relatives had a common HLA haplotype (A2, B8, DRw3). However, in the other two reports, no consistent HLA associations were found. The monoclonal IgM light chain type may differ between relatives with familial Waldenstrom macroglobulinemia, as occurred in monozygotic twins with Waldenstrom macroglobulinemia (Fine et al. 1986). Autoimmune disorders and immunoglobulin abnormalities are frequent in relatives of patients with familial Waldenstrom macroglobulinemia, suggesting that in these families Waldenstrom macroglobulinemia may be one manifestation of a genetic predisposition to abnormal immunoglobulin synthesis control mechanisms (McMaster 2003). Linkage of WM to chromosome 4q has been described (McMaster et al. 2006). Only 4 of 200 healthy controls (2 %) were found to be carriers of paratarg-7 (pP-7), whereas pP-7 carrier state was associated with a significantly increased risk (odds ratio=6.2;  $P=.001$ ) for developing IgM-MGUS/Waldenstrom macroglobulinemia. The pP-7 carrier state is inherited as a dominant trait. After IgA/IgG-MGUS and multiple myeloma, IgM-MGUS/WM is the second neoplasia associated with pP-7 carrier state (Grass et al. 2011).

## Histiocytoses

This is a heterogeneous group of disorders characterized by abnormal proliferation of histiocytes, and nonmalignant histiocytic disorders are subdivided into two major types: (1) Langerhans' cell histiocytosis (including histiocytosis X, eosinophilic

granuloma, Letterer–Siwe disease, and Hand–Schuller–Christian disease and are characterized by the presence of the Birbeck granule) and (2) hemophagocytic syndromes (which include familial erythrophagocytic lymphocytosis, also known as familial lymphohistiocytosis or familial reticuloendotheliosis).

Langerhans cell histiocytosis (LCH) is considered a nonhereditary disorder but rarely may be familial (Arico et al. 1999). Most such cases are in monozygotic twins and the concordance rate is 85 % (this does not necessarily indicate genetic factors as in utero spread via intraplacental anastomosis cannot be excluded).

A hereditary predisposition to B cell proliferative diseases has been established, and IgG/A and IgM disorders may occur together in families, where enhanced B cell responsiveness may be found in healthy subjects clustered around cases (Steingrimsdottir et al. 2011).

Familial hemophagocytic lymphohistiocytosis is a rare autosomal recessive disorder (1.2 cases/million children each year), which usually presents in early childhood (80 % by the age of 2 years) with failure to thrive, fever, anemia and hepatosplenomegaly and, histologically, multisystem (liver, spleen, lymph nodes, bone marrow, central nervous system) lymphohistiocytic infiltrates. Without treatment the prognosis is very poor. Familial hemophagocytic lymphohistiocytosis is a heterogeneous disorder. Mutations in the perforin gene account for >30 % of cases, and about 10 % are linked to the chromosome 9 FHL1 locus (Goransdotter Ericson et al. 2001). Recently mutations in hMunc13-4, a member of the Munc13 family of proteins involved in vesicle priming function, were identified in a further subset of familial hemophagocytic lymphohistiocytosis (FHL3). Inactivation of hMunc13-4 causes defective exocytosis of perforin containing lytic granules (Feldmann et al. 2003). Other genes that may be involved in different families include *RAG1* and *RAG2*, the syntaxin-11 gene, and syntaxin-binding protein 2.

An autosomal recessive form of histiocytosis associated with sensorineural deafness and joint contractures, Faisalabad histiocytosis, has been mapped to 11q25. Further genetic heterogeneity in familial hemophagocytic lymphohistiocytosis was suggested by a study in which FHL in 2 unrelated Canadian families with affected first cousins was not linked to 9q21.3-q22 or 10q21-q22 (Graham et al. 2000).

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## Chapter 9

# Musculoskeletal System

### Bone Tumors

In general, sarcomas of bone, muscle, or connective tissue are rare, especially in children. Bone tumors comprise about 5 % of childhood cancers (3 % osteosarcomas and 2 % Ewing sarcoma), and their incidence overall is about 10 per million persons in the UK. The age-standardized rate of malignant bone tumors for white children (0–14 years of age) in the SEER Registry, 1983–1992, was 6.4 per million. Soft tissue sarcomas are slightly more common (10 per million). The rates are similar for black children in the same registry, except for Ewing sarcoma, which is nine times less common in black children (Parkin 1998).

### *Osteosarcoma*

Osteogenic sarcoma is commoner in males than in females and shows two age peaks, one at adolescence and a second, which parallels that of chondrosarcoma, in the sixth and seventh decades. The tumor has a predilection for rapidly growing bone, and the risk is increased in Paget disease (Wu et al. 1991). Children with osteosarcoma are significantly taller at time of diagnosis than are unaffected controls (Gelberg et al. 1997). A similar but not significant difference is seen for children with Ewing sarcoma. Familial aggregations of Paget's disease are sometimes seen; several loci have been implicated, and mutations have been detected in the *TNFRSF 11A* gene in affected individuals (Hughes et al. 2000).

Familial osteosarcoma is rare, but multiple cases have been described in a number of sibships. A study of familial osteosarcoma identified 59 affected individuals from 24 families. Seven patients had Paget disease, three had a history of multiple fractures, two had bilateral retinoblastoma, and one had an osteosarcoma at another site (Hillmann et al. 2000). Sarcoma-prone families have been reported where individuals with osteosarcoma had germline mutations in *TP53* (Lynch et al. 2003), and

about 3 % of children with osteosarcoma may carry germline mutations in *TP53*. They may not all have a substantial family history consistent with Li–Fraumeni syndrome (Toguchida et al. 1992; McIntyre et al. 1994).

Osteosarcoma may also occur in individuals with germline mutations of the retinoblastoma gene (relative risk up to 500 times normal), especially in the field of any irradiation (see p. 15; Mertens and Bramwell 1995). It may also occur in the multiple exostosis and multiple endostosis syndromes, Bloom syndrome (Fuchs and Pritchard 2002), and in Rothmund–Thomson disease (Cumin et al. 1996; Leonard et al. 1996). This disorder is characterized by skin atrophy, telangiectasia, hyper- and hypopigmentation, congenital skeletal abnormalities, short stature, premature aging, and a predisposition to malignancy. Truncating mutations in the causative gene, *RECQL4*, (Kitao et al. 1999; Simon et al. 2010) appear to be more strongly associated with osteosarcoma than are other types of mutations (Wang et al. 2003). However, mutations in *RECQL4* are uncommon in sporadic osteosarcoma (Nishijo et al. 2004). There has been a report of a family with familial gigantiform cementoma, where one individual developed an osteosarcoma (Rossbach et al. 2005).

There is a risk of malignant degeneration in both monostotic fibrous dysplasia (which is sporadic) and McCune–Albright syndrome, characterized by polyostotic fibrous dysplasia, cafe-au-lait skin pigmentation, and precocious puberty, in which activating mutations of Gs proteins (postzygotic mutations in the *GNAS1* gene) have been detected (see p. 275; Alman et al. 1996). Patients with polyostotic fibrous dysplasia are at higher risk of malignant degeneration than those with monostotic lesions, which is thought to reflect their greater number of lesions rather than an increased risk per lesion. Somatic mutations in GS alpha have been found in both conditions (Lumbroso et al. 2004; Pollandt et al. 2001). In genetically predisposed individuals (e.g., Li–Fraumeni syndrome), a second osteogenic sarcoma may develop in the field of radiation delivered to the initial primary cancer (Li et al. 1978). Osteogenic sarcoma occurs as part of the OSLAM syndrome, described in a single report of probable autosomal dominant inheritance of childhood osteosarcomas associated with erythroid mastocytosis and a megaloblastic marrow and limb abnormalities (Mulvihill et al. 1977).

Hereditary multiple exostoses (diaphyseal aclasis) is an autosomal dominant skeletal dysplasia with an estimated prevalence of 9 per 1,000,000 population. It is characterized by the development of numerous cartilage-capped exostoses in actively growing areas of bone (Ahn et al. 1995). The most common sites are the regions of the long bones, the pelvis, scapula, and ribs, but the skull and vertebrae are usually spared. A Madelung deformity of the forearm is common. The multiple exostoses produce bony deformities, abnormal bone growth, and mild short stature. Penetrance is almost complete radiologically but with many subclinical lesions. Growth of the exostoses is maximal during childhood and adolescence, and the diagnosis is usually made during the first decade of life. The major complication of this disorder is malignant degeneration of the exostoses. Estimates of this risk vary, but the incidence is probably less than 10 %. Patients should be alerted to the significance of a rapid change in the rate of growth and the development of pain and inflammation. Regular surveillance to detect these changes is recommended. If osteosarcomas occur, they develop at an earlier age than their sporadic counterparts,



at a mean age of approximately 30 years (range 10–50 years) (Hennekam 1991). The presence of multiple exostoses in a patient with a balanced translocation t(8;11)(q24.11; p15.5) led to the identification of one of three loci now identified, on chromosomes 8q24.1, 11p13, and 19p, in which germline mutations can cause this disorder (Ludecke et al. 1991; Wuyts et al. 1996). Germline mutations have also been identified in the *EXT1* and *EXT2* genes (Heinritz et al. 2009). Both genes encode glycosyltransferases that are involved in heparan sulfate biosynthesis. The risk for sarcoma is greater for those with *EXT1* mutations than for *EXT2* mutations. Multiple exostoses type III has been mapped to chromosome 19 (*EXT3*). Screening for sarcoma in *EXT1* mutation carriers is justified (Porter et al. 2004; Seki et al. 2001).

Multiple exostoses also occur in metachondromatosis, an autosomal dominant condition characterized by short stature, with exostoses and enchondromas occurring in the hands and long bones. The osteochondromas point towards the joint and there is a tendency for them to regress and even disappear. It is caused by mutations in the *PTPN11* gene on chromosome 12q24 (Sobreira et al. 2010).

The Langer–Giedion syndrome (trichorhinophalangeal syndrome type II) is characterized by postnatal short stature, sparse hair, unusual faces with pear-shaped nose and long philtrum, micrognathia and protruding ears, and multiple exostoses (Buhler et al. 1987). About 70 % of affected individuals have developmental delay. It is a contiguous gene syndrome on 8q24.1, involving loss of functional copies of the *TRPS1* and *EXT1* genes on chromosome 8q24 (Ludecke et al. 1995).

Exostoses–anetoderma–brachydactyly type E is probably an autosomal dominant disorder characterized by a combination of macular atrophy, multiple exostoses, and brachydactyly (Mollica et al. 1984).

A contiguous gene syndrome on chromosome 11p11, known as DEFECT 11, involves *EXT2*. In this condition, the multiple cartilaginous exostoses develop in the first few years of life, and increase in number until puberty is complete. They cause deformity and asymmetry of growth, and there is a small risk of osteosarcoma developing. This condition is usually sporadic.

## Chondrosarcoma

The incidence of this tumor increases with increasing age. Chondrosarcoma is described as a complication of multiple enchondromatosis (Ollier disease; see below), inherited multiple exostoses (diaphyseal achlasia; see above), Maffucci syndrome (p. 274; Hecht et al. 1997), and other conditions in which exostoses occur. The incidence of malignancy in these syndromes has been assessed as 18 % (Sun et al. 1985). Two groups have recently reported that somatic mosaic mutations in *IDH1* and *IDH2* are the predominant cause of both Ollier disease and Maffucci syndrome (Pansuriya et al. 2011; Amary et al. 2011).

Multiple enchondromatosis (Ollier disease) is usually sporadic, although several families with affected siblings have been described. Deformities, particularly of the long bones, develop because of the enchondromas, resulting in asymmetrical, bilateral limb shortening, bowing, or deformation. The enchondromas tend to grow until

adolescent growth is over. Sarcomatous degeneration (chondrosarcoma) can occur in the lesions in adult life, and intracranial gliomas (Chang and Prados 1994) and ovarian juvenile granulosa cell tumors and precocious puberty have also been described in this condition (Tamimi and Bolen 1984).

Maffucci syndrome, characterized by multiple enchondromas and subcutaneous hemangiomas, is associated with a high risk of malignant transformation, a risk of 30 % for chondrosarcomas and other malignancies being reported (Albrechts and Rapini 1995; Kaplan et al. 1993). Intracranial chordoma has also been reported in this syndrome (Nakayama et al. 1994). There was a suggestion that a single germline mutation in parathyroid hormone-related protein (*PTHRI*), c.448CT, resulting in R105C could be an important cause of endochondromatosis (Hoppyan et al. 2002), but a subsequent study did not find any mutations in *PTHRI* in patients with enchondromatosis (Rozeman et al. 2004).

Hereditary multiple exostoses, associated with germline mutations in the *EXT2* gene, predispose to familial chondrosarcoma (Hecht et al. 1997), and loss of heterozygosity is seen in the tumor in the region of chromosome 11 where *EXT2* maps (see above).

## Ewing Sarcoma

This tumor has a peak age at onset in adolescence, is rare in black races, and is not radiation induced. Its incidence is 1.7 per 1,000,000 per year. Familial cases are rare, and the tumor only rarely occurs as part of specific familial cancer syndromes. It is probably a member of a family of neoplasms that includes a skin tumors and primitive neuroectodermal tumors of bone and soft tissue. Retinoblastoma has been recorded as a first primary cancer in ten cases of Ewing sarcoma, and Ewing sarcoma has also occurred after leukemia and lymphoma (Coppes et al. 2001). An excess of inguinal hernias has been observed in children with Ewing sarcoma.

A t(11; 22)(q24; q12) translocation occurs in up to 95 % of Ewing sarcomas and also in primitive neuroectodermal tumors and in peripheral neuroepithelioma and Askin tumors. Some Ewing sarcomas without a t(11; 22) show more complex rearrangements or rearrangements involving 22q12 and other chromosomes so that, overall, 92 % of tumors have a 22q12 breakpoint and 88 % have a 11q23.3 breakpoint (Griffin et al. 1986). A der (16) t(1; 16)(q11; q11) has been observed in the later stages of tumor development (Mugneret et al. 1987). The result of the t(11; 22) is that an aberrant transcription factor protein is produced (Granwetter 1995; Lin et al. 1999). None of these genetic rearrangements are inherited.

## Rhabdomyosarcoma

Soft tissue sarcomas account for up to 8 % of all childhood cancers and 2 % of childhood cancer deaths, with an incidence of about 8 per 1,000,000 per year. About half occur in children aged under 3 years, with an equal sex incidence.

Rhabdomyosarcoma accounts for two-thirds of pediatric soft tissue sarcomas (McDowell 2003) and most commonly arise in the head and neck (40 %), genitourinary tract (20 %), and extremities (20 %) (Crist and Kun 1991). On histological criteria, rhabdomyosarcoma may be classified into two main subtypes: embryonal and botryoid (two-thirds of all tumors) and alveolar (one-third).

Most rhabdomyosarcomas are sporadic, but they complicate neurofibromatosis type 1 (NF1; see p. 288, Brems et al. 2009), the Beckwith–Wiedemann syndrome (p. 221) (Lapunzina 2005), and the Li–Fraumeni syndrome (p. 271). Segregation analysis for soft tissue sarcomas in the absence of a known genetic syndrome suggests a heritability of 0.13, due to a postulated rare autosomal dominant gene (population frequency 0.00002) with a penetrance of 50 and 90 % at ages 30 and 60 years, respectively. The risk to first-degree relatives is significantly increased if the index case has two or more primaries (Burke et al. 1991).

Germline mutations in *TP53* may be detected in around 10 % of children with rhabdomyosarcoma (Diller et al. 1995), especially orbital alveolar rhabdomyosarcomas, and rhabdomyosarcoma is the second most prevalent tumor in Li–Fraumeni syndrome after breast cancer (Olivier et al. 2003). Embryonal rhabdomyosarcoma (which occurs in 6 % of tumors in Beckwith–Wiedemann syndrome) specifically shows chromosome 11p allele loss in the same region as the Beckwith–Wiedemann gene. A translocation between chromosomes 2 and 13, (2; 13)(q37; q14), has been described specifically in rhabdomyosarcoma (Meddeb et al. 1996); although it is most frequent in alveolar rhabdomyosarcoma, it has also been reported in embryonal and undifferentiated types. Embryonal rhabdomyosarcomas are the most common tumor associated with Costello syndrome (Gripp 2005), and they may also be seen in children with any of the “RASopathies” (i.e., with germline mutations in genes which are part of the Ras/mitogen activated protein kinase (MAPK) pathway), including Noonan, LEOPARD, and cardio-cutaneous-facial syndromes (Tidyman and Rauen 2009; Denayer et al. 2010). They also have been described in individuals with biallelic *PMS2* mutations (Kratz et al. 2009) and in Nijmegen breakage syndrome (Meyer and Spunt 2004) embryonal rhabdomyosarcomas are also reported in *DICER1* mutation carriers, particularly those arising from the cervix (Foulkes et al. 2011).

## Other Sarcomas

Synovial sarcomas occur in adolescents and young adults, especially males, have no racial predilection, and are not noted for familial occurrence. The tumors have been shown to have X:18 chromosomal translocations t(X:18)(p11.2; q11.2), involving a breakpoint at Xp11.2, resulting in the formation of a hybrid transcript (Gilgenkrantz et al. 1989; de Leeuw et al. 1995; Carbone et al. 2002; de Leeuw et al. 1994).

A study of the family histories of children with soft tissue sarcomas showed an increased family history of the Li–Fraumeni syndrome, sarcomas, gastric cancer, and neurofibromatosis, and it was considered that one-third of cases had a genetic susceptibility (Hartley et al. 1993).

Extraskelatal myxoid chondrosarcomas have been found to show a 9:22 chromosomal translocation: t(9; 22)(q31; q12.2) causing a *NR4A3/TFG* fusion gene (Hisaoka et al. 2004).

Kaposi sarcoma (multiple idiopathic pigmented hemangiosarcoma) has rarely been described in several members of the same family, suggesting an autosomal dominant pattern of inheritance. The condition is characterized by red–purple nodules, plaques, and macules which are commonest on the extremities but can occur at any site, including internally. Edema is associated, due to tumor infiltration of lymphatics, and the lesions spread, often with metastatic dissemination, usually with fatal results, although spontaneous regression has been described. The condition is commoner in people of Italian or Jewish origin (DiGiovanna and Safai 1981). Kaposi sarcoma is usually sporadic and immunosuppressed transplant recipients; it is the most common neoplasm affecting patients with AIDS, and HIV infection is an important risk factor in its development: the KS risk of AIDS patients is 20,000-fold over that of the general population. Foster et al. (2000) found a strong association between the IL6 gene promoter polymorphism and susceptibility to Kaposi sarcoma in HIV-infected men. Homozygotes for IL6 allele G, associated with increased IL6 production, were overrepresented among patients with Kaposi sarcoma, whereas allele C homozygotes were underrepresented. A novel herpes virus, termed KS-associated herpes virus (KSHV) or human herpes virus 8 (HHV8), has been detected in Kaposi sarcoma tissues, indicating that a viral infection may be important in the etiology of this condition (Kedes et al. 1996).

Uterine leiomyomas (fibroids) occur in individuals with leiomyomatosis, where germline mutations in the fumarate hydratase (FH) gene predispose to these tumors and to type 2 papillary renal cell cancer (see p. 201).

## Rhabdoid Tumors

Rhabdoid tumors are aggressive pediatric malignancies which mainly develop in infancy and early childhood. When they arise in the central nervous system, they are referred to as atypical tetratoid/rhabdoid tumors and malignant rhabdoid tumor (MRT) when they arise in other renal and extrarenal sites. Most are associated with loss of function of the *SMARCB1* gene in chromosome 22q11.2, and approximately one-third of patients with rhabdoid tumors have a germline mutation in the *SMARCB1* gene. Incomplete penetrance and gonadal mosaicism has been described in families with such mutations, and relatives of affected cases may develop rhabdoid tumors, schwannomas, or schwannomatosis (Eaton et al. 2011).

## Sacroccygeal Teratoma

After the first few years of life, most teratomas are gonadal. Familial benign cystic teratoma of the ovary has been described in three generations of a family (Brenner and Wallach 1983). Adult testicular gonadal germ cell tumors tend to be aneuploid,

although infantile gonadal germ cell tumors may more often be tetraploid or diploid, which suggests that they may have a different etiology (Silver et al. 1994). In fact, most teratomas develop in the sacrococcygeal area and tend to be benign. There may be associated malformations of the sacrum, vertebrae, and gastrointestinal or urogenital tracts. Familial teratoma with an autosomal dominant mode of inheritance has been described, with variable penetrance, and some affected individuals have been described to have anterior sacral meningocele, sacral defects, or skin dimples without teratoma (Yates et al. 1983). The Currarino triad involves the association of partial sacral agenesis with intact first sacral vertebra (“sickle-shaped sacrum”), a presacral mass, and anorectal malformation. Some cases of the Currarino syndrome may be caused by mutations in the *HLXB9* homeobox gene (Kim et al. 2007).

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## Chapter 10

# Skin

Genetic predisposition to skin cancer is most frequently seen by dermatologists in a number of dominantly inherited conditions such as familial melanoma, the basal cell nevus syndrome, self-healing epitheliomas of Ferguson Smith, and Bazex–Dupré–Christol syndrome. There are also a number of rare skin diseases which are associated with chronic inflammation of the skin, such as epidermolysis bullosa which are associated with an increased risk of squamous cell carcinoma of the skin (SCC). These conditions will be discussed in the first part of this chapter (Tsai and Tsao 2004).

In the second part of the chapter, we will discuss inherited disorders where skin cancers occur but for which there are often more pressing medical implications, such as albinism, the chromosome breakage disorders (Bloom’s syndrome (p. 226), Fanconi anemia (p. 249), ataxia telangiectasia (p. 219), xeroderma pigmentosum (p. 320)), Cowden’s disease (p. 233), dermatitis herpetiformis/celiac disease, DiGeorge syndrome, familial hyperglucagonemia, Gardner’s syndrome (p. 256), the basal cell nevus syndrome (Gorlin syndrome) (p. 252), hemochromatosis, multiple endocrine neoplasia type 2 (MEN2B, p. 252), neurofibromatosis type 1 (NF1, p. 288), porphyria, tuberose sclerosis (p. 307), and tylosis (p. 312).

There are some additional dermatological disorders which show some clustering in families, which may rarely be associated with skin cancer, such as lichen planus or lichen sclerosus et atrophicus, but these are not discussed here.

## Specific Skin Cancers

With Julia A. Newton-Bishop

## ***Genetic Predisposition to Melanoma***

Melanoma is a relatively uncommon cancer, with an incidence in most of Northern Europe of around 10 per 100,000 per annum (Parkin et al. 2001). In many countries, there is a sex difference in incidence so that in some, particularly in the UK, it has been more common in women, whereas in hot countries it is more common in men. The incidence has increased markedly this century in white people in most Western countries and in Australia and New Zealand, which have the highest rates in the world, but melanoma is fortunately rare in Asian or black skin (Eide and Weinstock 2005). The disparity in incidence between white and pigmented skins gives the first clue that genetics play a major role in determining susceptibility to a form of cancer for which the major environmental determinant is sun exposure (Jones et al. 1999).

The commonest type of melanoma is the superficial spreading type, which has the appearance of a mole progressively changing in shape, size, and color. The melanomas commonly have irregularly distributed hues of brown, grey, black, or red. These tumors are most frequent on the lower leg in women and on the trunk in males. The prognosis is determined by the Breslow thickness in millimeters, which is the thickness measured by the histopathologist from the granular layer of the skin to the deepest part of the tumor, as well as sex, age, tumor site, and other histological features such as the presence of ulceration (Balch et al. 2009). Earlier diagnosis with thinner tumors is associated with a better prognosis (Rees 2003; Barsh 1996; Elwood et al. 1990; Bahmer et al. 1990; Balch et al. 2001; Anderson and Badzioch 1991; Augustsson et al. 1990; Hayward 2003).

Epidemiological studies have established that the most potent phenotypic risk factor identified to date is the presence of numerous or clinically atypical nevi or moles (Fig. 10.1). The presence of multiple nevi, some of which are clinically



**Fig. 10.1** Familial atypical mole-melanoma syndrome: a melanoma arising from a dysplastic or atypical nevus; note the irregular borders and pigmentation (Courtesy of Julia A. Newton-Bishop)

atypical, is called the atypical mole syndrome (AMS) phenotype (otherwise known as the dysplastic nevus syndrome (Tucker et al. 2002) or the familial atypical mole and multiple melanoma syndrome FAMMM (Bergman et al. 1992)). It was thought originally that this phenotype was indicative of the inheritance of high-penetrance melanoma susceptibility genes, but it is now recognized that the AMS is relatively common, for example, it was seen in 2 % of the general UK population in one study (Newton et al. 1993), and 18 % of healthy individuals had at least one clinically diagnosed atypical nevus in a Swedish study (Augustsson et al. 1991). The odds ratio for melanoma in individuals with the AMS but no family history of melanoma is in the order of 10 relative to those who have very few nevi at all (Bataille et al. 1996). The absolute risk to such people is therefore moderate. Twin studies have shown that nevi are predominantly genetically determined (Easton et al. 1991; Wachsmuth et al. 2001) and it is hypothesized that the AMS in the absence of a family history is indicative of genetic susceptibility to melanoma with some contribution from sun exposure (particularly sunny holidays). In recent times some of the associated genes have been found using genome-wide association studies (GWAS). Single nucleotide polymorphisms (SNPs) associated with nevus number and melanoma risk were in the *TERT* gene (Rafnar et al. 2009; Barrett et al. 2011), near to the locus coding for *CDKN2A* on chromosome 9 (Bishop et al. 2009) and on chromosome 22 in a gene known as *PLA2G6* (Bishop et al. 2009). *TERT* codes for telomerase, a polymerase which maintains the telomere end (or cap) which protects the chromosomes from end-to-end fusion, nucleolytic decay, and atypical recombination (Nan et al. 2011), so this observation is consistent with a previous study in which patients with more nevi had longer telomeres (Bataille et al. 2007). The biology which underpins the second two associations (on chromosome 9p and *PLA2G6*) is not yet fully understood. Finally, there is some evidence of a role for the gene coding for interferon regulatory factor 4 (*IRF4*) and nevus number and melanoma risk, but the nature of that relationship is apparently complex (Duffy et al. 2010), with age-dependent effects on nevus number. Even when all these genes are considered together, however, only about 3 % of the variation in nevus number is currently explained (unpublished Leeds in-house data) (Cannon-Albright et al. 1990; Auroy et al. 2001; van der Velden et al. 2001).

Other phenotypic risk factors relate to the presence of fair skin and hair, freckles, and a reported susceptibility to sunburn, often referred to as people's "skin type" (Gandini et al. 2005a, b). A major genetic determinant of this phenotype (and a genetic risk factor for skin cancer) is the inheritance of common polymorphisms of the melanocortin receptor 1 (*MC1R*) gene, which codes for variation in the melanocortin receptor to which MSH binds and which result in modulation of the ratio of eumelanin (black pigment) to pheomelanin (red/yellow pigment) in the skin and hair. The association was first reported by Valverde et al. (1996) but has been explored extensively by other groups working on sporadic melanoma (Raimondi et al. 2008) and familial melanoma (Demenais et al. 2010).

As genetically determined phenotypes associated with a tendency to burn in the sun have been unequivocally identified as melanoma risk factors, it is not surprising

that there is also an increased risk associated with environmental factors, such as a history of severe sunburn and sunbathing (Gandini et al. 2005a, b; Chang et al. 2009).

Additional pigment genes underlying phenotypic variation in skin and melanoma susceptibility have also been explored in GWAS, and these include *SLC45A2* (Barrett et al. 2011), the *IRF4* locus, the gene coding for tyrosinase (*TYR*) (Gudbjartsson et al. 2008; Barrett et al. 2011), and the agouti signaling protein locus *ASIP* (Barrett et al. 2011; Gudbjartsson et al. 2008) which is an agonist of the *MC1R* and therefore functions in the same pathway as variants in *MC1R* having effects on melanin synthesis. Using what is known about the variants of *MC1R*, it is apparent that we have in all now identified susceptibility genes which “explain” 30 % of the variance in skin pigmentation in white-skinned people taking part in the GWAS (unpublished data).

GWAS have identified a number of additional melanoma susceptibility genes which are not associated with either “at-risk” phenotype (fair skin or increased nevus number) which opens up new and interesting biological pathways to better understand melanomagenesis. These include *ARNT* (Macgregor et al. 2011) two genes involved in DNA repair, *PARP1* and *ATM*, *CASP8* (caspase 8 which is an apoptosis-related gene), *CCND1*, and *MX2* (Barrett et al. 2011).

Clustering of many cases of melanoma predominantly occurs in families in which there appears to be susceptibility to melanoma alone (see below). There are very rare families demonstrating susceptibility to both cutaneous melanoma and ocular melanoma. Scandinavian families have been reported in which susceptibility to ocular and skin melanoma was linked to a gene on 9p21 (Jonsson et al. 2005) and more recently, an inherited mutation in the *BAP-1* gene on chromosome 3p was reported in an ocular melanoma patient (Harbour et al. 2010).

Low numbers of cases of melanoma have also been reported in hereditary non-polyposis colorectal cancer (Lynch syndrome, p. 256). In one recent series, 9 family members developed melanoma from 8 families in a series of 60 Lynch syndrome families (Ponti et al. 2008). There is a reported increased risk of melanoma in the Li–Fraumeni syndrome (p. 271) and inherited retinoblastoma (p. 15). In inherited retinoblastoma many of the melanomas have been reported to occur in the radiation field. There is a clear increased risk in patients with xeroderma pigmentosum in whom DNA repair defects are causal (p. 320). Inheritance of *BRCA 2* mutations also appears to increase the risk of melanoma moderately (Liede et al. 2004).

Congenital anomalies such as neurocutaneous melanosis (Arunkumar et al. 2001; De Andrade et al. 2004) (p. 140) and giant congenital hairy nevi (p. 140) also predispose to melanoma.

## ***Familial Melanoma***

Rare families exist in which there is an increased risk of melanoma and in which the tendency to melanoma appears to be inherited as an autosomal dominant with incomplete penetrance, first recognized in the nineteenth century by Norris (1820). Within these families, the majority of melanomas are of the superficial spreading type, but

there may be less common types such as nodular melanomas and lentigo maligna melanomas. Ocular melanomas may occur in some families, but this is very rare (see above). In the UK families with the most common high penetrance susceptibility gene, *CDKN2A* so far reported, there is little evidence of increased susceptibility to cancers other than melanoma. However, other groups have reported an association in particular with pancreatic carcinoma, particularly in the Netherlands and in the USA (Bergman et al. 1990; Lynch and Fusaro 1991), and other gastrointestinal cancers (see below).

In the families described with a founder mutation in the *CDKN2A* gene in the Netherlands (de Snoo et al. 2008), the increased risk of pancreatic cancer in these families was very clear in a recent study, but there was also evidence of increased risk of other cancers related to smoking such as cancers of the lip, mouth, pharynx, and respiratory system. Insufficient numbers of families from other centers have so far been studied in order to quantify the risk of nonmelanoma cancers, but it is clear that some families have an increased susceptibility to gastrointestinal cancer as well as to melanoma, which is currently being explored by the Melanoma Genetics Consortium, GenoMEL ([www.genomel.org](http://www.genomel.org)). It would seem prudent to advise family members strongly against smoking.

Some melanoma families also have the AMS, but not all. In a proportion of families, this abnormal nevus phenotype in melanoma cases may be striking. The phenotype is characterized by the presence of clinically atypical moles (by definition more than 5 mm in diameter with an irregular or blurred edge and irregularly irregular pigmentation), numerous but otherwise banal moles, and moles in unusual places such as on the buttocks, in the iris, and on the ears (Newton et al. 1993). The biological significance, even within melanoma-prone families, of this phenotype is unclear as some families with melanoma do not have abnormal nevi at all. In the UK families so far described, the members of the largest family, with nine cases of melanoma, all had normal nevi (Harland et al. 1997). Overall, it is clear that although the atypical mole syndrome is associated in some way with familial melanoma, it is a poor indicator of gene carrier status and cannot be used reliably even within these melanoma families to predict who is a gene carrier (Wachsmuth et al. 1998; Newton Bishop et al. 2000).

In deciding how atypical mole syndrome patients should be managed in terms of follow-up and risk estimation then, family history is the key. Patients with this phenotype without a personal or family history of melanoma should be taught how to self-examine their nevi and be given advice about sun protection, but long-term follow-up is not normally appropriate. Patients with a strong family history of melanoma with or without the atypical mole syndrome should retain long-term access to the pigmented lesion service. The screening of nevi in patients with the atypical mole syndrome and a family history of melanoma is specialized, and all such patients should be referred to the local Cancer Centre Pigmented Lesion Clinic, usually run by a dermatologist. In such clinics, the emphasis is on clinical and dermoscopic examination of nevi, using photography for baseline documentation. Nevi are removed only if they appear to be changing, and therefore if malignant change is suspected, they are not excised prophylactically. Additional genetic counseling may be required.

Progress has been made in understanding the genetic basis of high-risk susceptibility. Initial reports of genetic linkage in melanoma families to chromosome 1p

(Bale et al. 1989a, b) have not yet been substantiated by other groups. Strong evidence of linkage to chromosome 9p, reported by the Utah group (Cannon-Albright et al. 1992), was soon confirmed by others although genetic heterogeneity exists. The tumor suppressor gene *CDKN2A*, which codes for the cyclin-dependent kinase (CDK) inhibitor p16, lies in the identified area of 9p, and all groups working on familial melanoma have now identified germline mutations in this gene so that to date the *CDKN2A* gene remains the major identified cause of high-risk familial melanoma. Overall, germline mutations in this gene have been identified in around 40 % of families with three or more cases of melanoma but much less frequently in families with only two cases. GenoMEL estimates an overall *CDKN2A* mutation penetrance for melanoma of 0.30 (95 % confidence interval (CI)=0.12–0.62) by age 50 years and 0.67 (95 % CI=0.31–0.96) by age 80 years, with evidence of greater penetrance where gene carriers live in sunnier climates, namely, Australia (Bishop et al. 2002). The confidence intervals for these estimations remain high so that GenoMEL will continue to improve its data. It has also been demonstrated that penetrance is higher in mutation carriers who also have certain *MC1R* polymorphisms (associated with a tendency to burn in the sun) (Demenais et al. 2010). Where *CDKN2A* mutation carriers have been ascertained from populations other than family studies, then the penetrance is predictably lower: the risk of melanoma in *CDKN2A* mutation carriers was approximately 14 % (95 % CI=8–22 %) by age 50 years, 24 % (95 % CI=15–34 %) by age 70 years, and 28 % (95 % CI=18–40 %) by age 80 years in the GEM study (Begg et al. 2005; Soufir et al. 2000; Newton Bishop et al. 1994; Lal et al. 2000; Bartsch et al. 2002; Goldstein et al. 1994, 2004).

As above, in some families with germline mutations in *CDKN2A*, there is also an increased susceptibility to pancreatic carcinoma, manifest in patients over the age of 45 years (de Snoo et al. 2008). This appears to be particularly seen in families with truncating mutations such as the founder p16-Leiden mutation, but is also seen in families with the founder mutation G101W, common in Italy and France (Ghiorzo et al. 2007). Most of these G101W families in which pancreatic cancer was seen also had melanoma, but very rare mutation-positive families were reported with pancreatic cancer alone (Ghiorzo et al. 2004). In the p16-Leiden families, the incidence of pancreatic cancer was reported to be 29 times greater than population levels, and more recently a lifetime risk of 17 % was suggested. In the Italian G101W families, a 9.4-fold risk (95 % CI 0.8–5.7) was reported. The elevated risk in the p16-Leiden families is sufficiently high that MRI screening is being investigated in clinical trials as a means of early detection of pancreatic cancer.

GenoMEL has reported the predictors of *CDKN2A* mutation detection in melanoma families and shown that early age of onset, multiple primaries, multiple cases of melanoma, and the presence of pancreatic cancer are all associated with an increased probability of finding mutations (Goldstein et al. 2007), although there was no significant evidence of increased risk of pancreatic cancer risk in Australian families with *CDKN2A* mutations (Loo et al. 2003; Bishop et al. 2000; Della Torre et al. 2001; Gillanders et al. 2003; Harland et al. 2000).

There has been some suggestion of an increased risk of breast cancer in *CDKN2A* mutation-positive women (Borg et al. 2000), but this is unsubstantiated as yet and the



risks of this and other cancers will be addressed by GenoMEL. Although families are reported in which both ocular and cutaneous melanomas occur (see above), there is no evidence of an increased risk of ocular melanoma in *CDKN2A* mutation carriers.

Germline mutations in *CDKN2A* have been identified in around 10–15 % of melanoma patients with multiple primaries. The prevalence of germline mutations in sporadic “population” ascertained melanoma cases however is low: in the GEM study, an identifiable mutation was identified in 1–2 %, depending on region of origin (Begg et al. 2005).

A second high-penetrance susceptibility gene was identified in 1996 when Dracopoli identified two families with the same single base pair substitution in another gene that coding for CDK4, producing a protein anomaly at the site at which p16, the *CDKN2A* product, binds (Zuo et al. 1996). Germline mutations in this gene are extremely rare. To date, only around seventeen families worldwide have been described with these mutations (Molven et al. 2005; Goldstein et al. 2007; Pjanova et al. 2007; Puntervoll et al. 2013).

However, the identification of the mutations strengthens the observation that the p16 protein is critical to melanoma carcinogenesis. Puntervoll et al. (2013) have recently reported that families with inherited *CDK4* mutations have a very similar clinical picture to those with *CDKN2A* mutations suggesting that the *CDK4* gene should be screened as well as *CDKN2A* in families who elect to proceed to gene testing.

Reported evidence of linkage to 9p in melanoma families in whom *CDKN2A* mutations could not be identified suggested that other *CDKN2A* mutations remained to be found. There was however no evidence for promoter mutations except for a mutation of the *CDKN2A* 5'UTR which creates an aberrant initiation codon which has been identified in a number of families in North America, Australasia, and Europe (Liu et al. 1999). Splice site variants have been found (Harland et al. 2001, 2005) and 9p deletions (Mistry et al. 2005), but still a good proportion of melanoma families have no identifiable mutations.

*CDKN2A* is an unusual locus with an alternative reading frame coding for another protein p14ARF, whose role in melanoma carcinogenesis remains of great interest. In 1998 families with a susceptibility to melanoma and neural tumors were described in whom there were germline deletions at 9p (Bahau et al. 1998) and the suggestion was that there was loss of *CDKN2A* and exon 1 $\beta$ , coding for p14ARF. More recently, a similar family was reported in which the deletion appeared to result in loss of exon 1 $\beta$  only, (Randerson-Moor et al. 2001) with no evidence of resultant impact on p16. This, the first evidence that *p14ARF* is the third high-penetrance melanoma susceptibility gene, was strengthened when a germline mutation in exon 1 $\beta$ , which creates an abnormal splice site, was reported in a melanoma family (Hewitt et al. 2002), and a small insertion affecting *p14ARF* was reported in a Spanish melanoma family (Rizos et al. 2001).

Overall then, the consensus is that there are 3 high-penetrance susceptibility genes effecting p16, CDK4, and p14ARF, and there is recent evidence for another at 1p22, with a probable role for *BAP-1* in families with ocular melanoma (Harbour et al. 2010). In the UK currently we have identified probable germline

mutations in 53 and 68 % of three or more and four or more case families, respectively (Harland, Bishop and Newton-Bishop unpublished). This figure is lower in some other centers, particularly in areas of high incidence where lower-penetrance genes may be more evident (Goldstein et al. 2007). It is thought likely therefore that familial clustering in hot countries where people of Northern European origin live, such as Australia, has occurred as a result of inheritance of multiple lower-penetrance genes (such as those associated with pigmentation and nevus at-risk phenotypes described above) and intense sun exposure. The identification of *BAP-1* germline mutations however means that remaining families might have “boutique” mutations, or mutations peculiar to their family or a very small number of families.

Gene testing within melanoma families is taking place but the uptake is very variable internationally (de Snoo et al. 2003; Newton-Bishop et al. 2010; Kefford et al. 2002). Leachman et al. have argued the case for genetic counseling based upon a rule of threes (three or more cases in the family or three or more primaries in an individual) (Leachman et al. 2009), but the value of gene testing remains unclear to many. A positive *CDKN2A* mutation test may ultimately be of value when screening for pancreatic cancer has been shown to be effective and for families in which pancreatic cancer has occurred. There is a European screening research program called EUROPAC addressed to this issue. In the absence of pancreatic cancer, however, a positive test is unlikely to change management. As causal mutations are currently not identifiable in many families even with multiple cases of melanoma, the possibility is that there are as yet unidentified mutations, so that a negative test result is of limited utility. An online package for genetic counselors has been placed on the GenoMEL website, [www.genomel.org](http://www.genomel.org).

The majority of the *CDKN2A* mutations identified to date appear to co-segregate with the tumor, and from what is known about the structure of the p16 protein, it is to some extent possible to predict which mutations are real and which are silent. P16 (INK4A) is a member of a family of CDK inhibitors, the other members of which are p15 (INK4B), p18 (INK4C), and p19 (INK4D). The members of the group have significant sequence homology and have a structure dictated by the presence of four or five so-called ankyrin repeats. Mutations which fall outside the ankyrin repeats were thought likely to be nonsignificant having a lower likelihood of impacting on the protein, like the common *CDKN2A* polymorphism Ala148Thr. Some splice site variants outside these repeats are however increasingly being recognized. In order to prove that identified mutations are significant, functional tests of the p16 protein have been developed. The test most widely used is a test of the ability of the mutant protein to bind to CDK4 and CDK6. But it is not a comprehensive test of function. For mutations described in large families around the world such as Arg24Pro, Met53Ile, and 23ins24, there is confidence that the mutations are real and that gene testing would produce interpretable results. For novel mutations, an abnormal functional test result would seem to be necessary before testing. GenoMEL maintains a database of these mutations (eMelanoBase) which is now part of LOVD (Leiden Open Variation Database) <http://chromium.liacs.nl/LOVD2/home.php>.

## ***Giant Congenital Melanocytic Nevus***

One percent of newborn infants has small congenital melanocytic nevi, but fortunately giant nevi (defined as 20 cm in diameter or larger) are very rare, estimated in one study to be one in 20,455 live births (Castilla et al. 1981). Most cases are sporadic and are thought to arise as a result of a post-zygotic mutation, possibly in the *NRAS* gene (Phadke et al. 2011). Very rare cases have been reported of more than one case in the same extended family where the mode of inheritance was postulated to be a polygenic paradigm pattern of inheritance (de Wijn et al. 2010). The risk of melanoma in congenital nevi is unclear due to its rarity, and publication bias and the published estimates of this risk for giant nevi range from 2 to 14 % (Shah 2010; Yun et al. 2012), with a significant proportion of melanomas occurring in the first 10 years of life (Shah 2010; Araim et al. 2004; Angelo et al. 2001; Makkar and Frieden 2002; Ruiz-Maldonado et al. 1992; Hoanq et al. 2002).

Imaging using MRI may identify anomalies in the CNS: both intracranial melanosis and others (Kinsler et al. 2001). Neuromelanosis may be complicated by hydrocephalus or other neurological symptoms (Kinsler et al. 2001). A very small proportion of neuromelanosis eventuates in intracranial melanoma, but the incidence is not established.

## ***Basal Cell Carcinoma (BCC)***

This epithelial tumor arises from the basal layers of the epidermis and its appendages (Fig. 10.2).

It is locally invasive, metastasis being excessively rare. It is the most common skin tumor affecting light-skinned people and appears predominantly in sun-exposed areas of the skin (head and neck predominantly although also on the trunk). It is indeed the commonest cancer overall. Arsenic is a known predisposing



**Fig. 10.2** The typical appearance of a BCC

environmental agent (Boonchai et al. 2000) but is now a rare cause. BCC may occur after radiotherapy: it was seen in the past as multiple lesions on the scalp as a sequel of the use of radiotherapy to treat scalp ringworm and now is seen more commonly as a late result of radiotherapy to treat cancer or even noncancerous conditions such as ankylosing spondylitis. The clue to the cause is the distribution so that multiple lesions in a rectangular distribution along the spine, for example, are more likely to be related to radiotherapy than genetic susceptibility. In a recent registry-based study from the Netherlands of 444,131, histologically confirmed cases between 1973 and 2008, age-adjusted incidence rates (European Standard Population) increased approximately threefold from 40 to 148 per 100,000 in males and from 34 to 141 in females. Lifetime risk of BCC was 1 in 5–6 for Dutch citizens (Flohil et al. 2011).

Most cases of BCC are sporadic but there is some evidence for clustering in families (de Zwaan and Haass 2010), and association studies have shown a similar relationship to pigment genes as for melanoma. Red-haired individuals are particularly sun sensitive, and therefore it is not surprising that variants in genes associated with red hair are associated with increased risk such as the melanocortin 1 receptor gene (*MC1R*) (Scherer et al. 2008; Han et al. 2006; Bastiaens et al. 2001a, b; Box et al. 2001a, b) and the agouti signaling protein locus (*ASIP*) (Nan et al. 2009). Polymorphisms in other pigment genes are also associated with risk such as the oculocutaneous albinism A2 gene *OCA2* (Box et al. 2001a, b) *SLC45A2* (Stacey et al. 2009a, b) and the interferon regulator gene 4, *IRF4* (Han et al. 2011). Loci not known as yet to be associated with pigmentation but which have been shown to be associated with susceptibility in GWAS include a gene coding for keratin 5, a locus near to the *CDKN2A* locus at 9p and *TERT* which codes for telomerase and therefore impacts on telomere length (Stacey et al. 2009a, b; Baird 2010). BCC and melanoma are therefore both associated with pigment genes, and it is not therefore surprising that patients not infrequently get both (Farndon et al. 1992; Gorlin 1984; Guarneri et al. 2000; Happle 2000).

Genetic disorders associated with a predisposition to basal cell carcinoma include Gorlin syndrome (the nevoid basal cell carcinoma syndrome) (p. 252) in which a characteristic facies, bony anomalies, odontogenic dental cysts, and palmar pits precede the development of multiple BCC. The number of BCC is increased in those with greater sun exposure, and radiotherapy significantly increases tumor risk both in the skin and the meninges and therefore must be avoided if at all possible. Rarer tumors include medulloblastoma and ovarian fibromas. In the UK, around 1 in 30,827 people is affected (prevalence) (Evans et al. 2010). Inherited mutations in the “patched” *PTCH1* gene at 9p 22.3 have been shown to be the cause of the nevoid basal cell carcinoma syndrome (Hahn et al. 1996; Johnson et al. 1996), loss of the second allele of *PTCH1* occurring somatically to cause BCC in gene carriers over time. Patched is a negative regulator of the hedgehog pathway which is a proliferative signaling pathway which is now known to be important in a number of cancers as well as BCC (de Zwaan and Haass 2010). Sporadic basal cell carcinomas show chromosome 9q allele loss, and mutations in the “patched” gene which causes the basal cell nevus syndrome have been detected with high frequency in such



**Fig. 10.3** Follicular atrophoderma (ice pick marks) in Bazex–Dupré–Christol syndrome

tumors. This supports the view that the “patched” gene is a gatekeeper for common skin cancers. Patched controls the activity of “smoothened,” and recent therapeutic developments for BCC have included the exploration of smoothened inhibitors (Skvara et al. 2011) for the treatment of very advanced disease.

Increased susceptibility to BCC is also seen in xeroderma pigmentosum (p. 320), porokeratosis, albinism, Bazex–Dupré–Christol syndrome (p. 187), and the rare Rombo syndrome (p. 189) (Van Steensel et al. 2001).

### ***Bazex Syndrome (Bazex–Dupré–Christol Syndrome)***

This trait (not to be confused with the nongenetic paraneoplastic acrokeratosis also described by Bazex, in which psoriasiform changes develop on the hands, feet, and face, with abnormalities of the nails associated with internal malignancy) is characterized by follicular atrophoderma, especially on the face, hands, feet, and elbows, with the appearance of “ice pick” marks (especially on the dorsum of the hands) (Fig. 10.3) but without palmar or plantar pits and multiple milia



**Fig. 10.4** Milia on the dorsa of the hands in a baby with Bazex–Dupré–Christol syndrome



(Fig. 10.4) (Kidd et al. 1996; Vabres et al. 1995). That the disorder is fundamentally one affecting the hair follicle is illustrated by the presence of hypotrichosis in affected individuals which is obvious from infancy. As in the basal cell nevus syndrome, affected children may develop benign proliferations of the hair follicle such as trichoepitheliomas (Yung and Newton-Bishop 2005a, b) in early in life. Multiple basal cell carcinomas may develop on the face from the second decade, but there is variable expressivity which is likely to be related to the degree of sun protection given in childhood. Occasional children develop pigmented proliferative lesions described as BCC (Abuzahra et al. 2011; Parren et al. 2011), but the author's experience is that these are difficult to distinguish from “benign” proliferations described by some as trichoepitheliomas. Bazex–Dupré–Christol syndrome is inherited as an X-linked dominant trait, both males and females being affected, and is linked to DXS1192 at Xq14–q27.1 (Abuzahra et al. 2011; Parren et al. 2011).

## ***Rombo Syndrome***

Rombo syndrome is a very rare syndrome (Ashinoff et al. 1993), first described in a four-generation family, in which affected individuals developed follicular atrophy of the skin of the cheeks in childhood. In affected adults, telangiectasia and skin papules appeared, especially on the face, and the eyelashes and eyebrows were abnormal. Basal cell carcinomas occur frequently from the third decade. The clinical description bears many similarities to Bazex–Dupré–Christol syndrome described above. Parren et al. believe the two conditions to be similar but different as Rombo syndrome was reported with male-to-male transmission and is therefore thought to be an autosomal dominant trait (Parren and Frank 2011).

## ***Squamous Cell Carcinoma (SCC)***

This tumor is derived from epidermal keratinocytes. The incidence of squamous cell carcinoma shows marked geographical variation. It is most frequent in parts of the world where light-skinned people are exposed to large cumulative exposures to sunlight. Thus, it is much more frequent in southern than northern states of America, in outdoor workers, and the incidence is much higher in light-skinned than in dark-skinned peoples (Carrucci 2004). Genetic variation accounting for pigmentation of the skin and reaction to sun exposure as described above is therefore also thought to be important in determining susceptibility. Albino individuals are particularly at risk, especially if they live in the tropics. Arsenic, tar, and oil derivatives and X-rays and gamma rays also predispose to squamous cell carcinoma. In the UK, SCCs occurring as a result of exposure to these carcinogens have become significantly less common as working conditions in relevant industries have improved. Squamous cell carcinomas are more common in chronically immunosuppressed individuals, and organ transplant recipients now represent a significant proportion of patients with multiple SCC. There is some evidence that the risk is particularly high in those treated with azathioprine as a result of higher incorporation of a metabolic product of azathioprine into skin cell DNA (Kalra et al. 2011), and the move to replacing this drug with others may reduce the incidence in the future.

SCC may also arise in chronic scars, ulcers, and sinuses, but as these chronic conditions are better controlled, this is now much less frequent in the developed world. SCC are still seen however in medical conditions where scarring cannot be controlled such as hereditary skin disorders that cause blistering and ulceration (e.g., epidermolysis bullosa) and conditions associated with leukoplakia, such as dyskeratosis congenita and lichen sclerosus et atrophicus.

Squamous cell carcinoma may also occur in the ectodermal dysplasias, the Rothmund–Thomson syndrome, sclerolytosis, and hyperkeratosis lenticularis perstans. Genetic disorders predisposing to cutaneous squamous cell carcinoma may also predispose to squamous cell carcinoma in the mucous membranes, e.g.,



dyskeratosis congenita and ectodermal dysplasia can predispose to tongue, esophageal, and cervical carcinoma.

### ***Epidermodysplasia Verruciformis***

Epidermodysplasia verruciformis (EV) is a rare inherited skin condition in which there is defective immunity to the human papillomavirus (HPV). It usually appears to be recessively inherited, but the genetic basis for the disorder is not entirely clear and in some families the pattern of inheritance is not consistent with a recessive pattern of inheritance (Robati et al. 2009). In some chronically immunosuppressed patients such as HIV-positive patients, phenocopies may be seen (Jacobelli et al. 2011). Affected individuals develop plane (flat) viral warts in childhood on the trunk and extremities, which evolve into verrucous, polymorphic, warty lesions over time. The appearance of some of the lesions is said to resemble pityriasis versicolor or basal cell papillomas on the trunk and actinic keratoses (precancerous lesions) on exposed sites (Vohra et al. 2010). Ultimately SCC may develop within the warty plaques which may metastasize (Vohra et al. 2010; Kim et al. 2010).

Numerous HPV subtypes have been identified in affected patients, and it is reported that lesions infected with HPV 5 and 8 are more likely to transform, but rarely others are described such as HPV-22b in EV-related SCC (Kim et al. 2010).

The gene associated with recessively inherited EV was mapped to two loci, 2p21-2p24 and 17q25, and subsequently nonsense mutations in two adjacent novel genes, *EVER1* and *EVER2*, that are associated with the disease were reported at 17p25 (Ramos et al. 2002). The EVER proteins are expressed by a number of cell types involved in immunity, e.g., dendritic cells and lymphocytes (Rezaei et al. 2011). Twenty-five percent of EV patients have no identifiable mutations in either *EVER1* or *EVER2* (Orth 2006).

### ***Ferguson-Smith-Type Self-Healing Epithelioma (Multiple Self-Healing Squamous Epithelioma)***

This is a rare, dominantly inherited disorder, which was first reported in people of Scottish descent, from Ayrshire (Shaw Dunn and Ferguson Smith 1934). It was thought that all cases are possibly descended from one individual (a founder effect), but recently the causal gene has been identified (*TGFBR1*) on chromosome 9q31-32 (Bose et al. 2006; Goudie et al. 2011a), and several different mutations were identified indicating that this is not so. Loss of function mutations in the *TGFBR1* gene has been found to underlie the disease. Interestingly missense mutations in this gene cause Marfan-related disorders with vascular involvement but no cancer susceptibility (Goudie et al. 1991, 2011a, b).

The condition is characterized by the postpubertal appearance of multiple cutaneous keratoacanthomas (Fig. 10.5), which enlarge, ulcerate, and eventually

**Fig. 10.5** A keratoacanthoma on the ear of a lady with self-healing epitheliomas of Ferguson Smith



heal, sometimes with calcification, to leave pitted, irregular scars which can be very disfiguring. Most lesions occur on the head and neck, in exposed areas of skin, especially where pilosebaceous follicles are found. The lesions resemble squamous cell carcinomas, but metastasize only very rarely (to lymph nodes) and do not generally behave in an aggressive fashion. In the past, treatment for the lesions (e.g., radiotherapy) has appeared to increase the invasiveness of the tumors as has been reported in the basal cell nevus syndrome as described above (Robertson et al. 2010; Orlow 1997; Griffiths 2002; Shiflett et al. 2002; Ward et al. 2002). There is marked variation in the age at onset and number of lesions in different affected individuals. Rarely tumors are seen in extracutaneous sites in affected patients, such as anal tumors and SCC like lesions of the vulva. Management is by sun protection, which is important (without resulting in vitamin D deficiency), and the avoidance of radiotherapy was possible. The use of acitretin has been reported for advanced disease (Robertson et al. 2010), and this has been found to be helpful in controlling cutaneous lesions.

## Inherited Conditions Predisposing to Dermatological Malignancy

### *Albinism*

Oculocutaneous albinism is a group of autosomal recessively inherited disorders of melanin synthesis, whose clinical manifestations are pale skin, white hair, nystagmus, and photophobia. There is considerable genetic heterogeneity, many distinct types having been described. Actinic skin damage, squamous cell carcinoma, and basal cell carcinoma are well-recognized complications of oculocutaneous albinism; malignant melanoma is a much less common complication.

Any patient with albinism is at an increased risk of cutaneous malignancies. This susceptibility to cancer appears to be related to the lack of skin pigmentation and attests to the protective qualities of melanin. However, in patients with vitiligo or piebaldism, areas of skin where melanin (and melanocytes) is absent do not appear to be predisposed to malignancies in the same way individuals with albinism should avoid sunlight exposure and use sunscreen creams when they are exposed to it (Iannello et al. 2003; Karim et al. 2002).

### *Birt–Hogg–Dubé Syndrome* (See p. 224)

This autosomal dominant condition is characterized by skin fibrofolliculomas, lung cysts, and a predisposition to spontaneous pneumothorax. These patients are at increased risk of developing renal neoplasms, most commonly chromophobe and oncocytic hybrid tumors. The gene responsible, *FLCL*, maps to chromosome 17 (Schmidt 2004).

### *Brooke–Spiegler Syndrome (Multiple Cylindromatosis)*

This is an autosomal dominant condition. It is characterized by multiple benign tumors of the skin appendages. These are smooth, dome-shaped, firm, pink tumors of the head (turban tumors), including syringomas and trichoepitheliomas and sometimes spiroadenomas, which develop from early adulthood and may be very disfiguring. Basal cell epitheliomas may develop in the lesions, and radiation therapy may exacerbate this tendency (Sze pietowski et al. 2001; Welch et al. 1968).

The tumors are of hairy skin and are not associated with basal or squamous cell carcinomas. The condition has been linked to chromosome 16q12–13 (Biggs et al. 1995; Fenske et al. 2000), and mutations in the *CYLD* gene have been identified as causing the condition. Genotype–phenotype correlations have not been

described until recently, when in a family with mild disease (where the tumors tended to be small), the causative mutation was R758X in the *CYLD* gene (Oiso et al. 2004; Blake and Toro 2009). Loss of the cylindromatosis tumor suppressor inhibits apoptosis by activating NF- $\kappa$ B. It has been suggested since aspirin also inhibits the action of NF- $\kappa$ B, it is a logical (topical) therapeutic agent for cylindromatosis, and phase 1 clinical trials of this are currently underway (Gutierrez et al. 2002; Bernends 2003; Brummelkamp et al. 2003; Lakhani 2004).

### ***Cheilitis Glandularis***

This rare condition, which can be inherited as an autosomal dominant trait, is characterized by diffuse nodular enlargement of the lower lip, with hypertrophy of the labial mucous glands, chronic inflammation, and dilatation of the excretory ducts. There is a high risk of squamous cell carcinoma of the lower lip (Vernia 2003).

### ***Chronic Mucocutaneous Candidiasis Syndrome***

This is a rare condition characterized by chronic and recurrent *Candida* infections of the skin, nails, and oropharynx from early childhood. There may be an underlying immune defect. In over 50 % of cases, there is associated endocrine disease. Several examples of familial chronic mucocutaneous candidiasis syndrome have been recorded, some showing an autosomal recessive and some an autosomal dominant mode of transmission; some cases are not associated with endocrinopathy (Buzzi et al. 2003). Late-onset cases may be sporadic. The condition can predispose to malignancy, especially of the oropharynx. The *Candida* endocrinopathy syndrome includes hypoparathyroidism, hypothyroidism, hypoadrenocorticism, and diabetes, usually autosomal recessive in inheritance (Ahonen 1985; Coleman and Hay 1997; Buzzi et al. 2003; Myhre et al. 2004). Vertical transmission of the syndrome with hypothyroidism has been described (Kirkpatrick 1994), and a syndrome of immune deficit, mucocutaneous candidiasis, and thyroid disease has been mapped to chromosome 2p in one family. A germline mutation in the *AIRE* gene has been described in a patient with this condition and muscular atrophy (Sato et al. 2002). An immune deficit causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. The autosomal recessive form of familial chronic mucocutaneous candidiasis (CANDF2) is caused by mutation in the *CARD9* gene on chromosome 9q34 (Glocker et al. 2009). Autosomal dominant candidiasis (CANDF1) maps to chromosome 2p, CANDF2 is caused by mutations in the *CARD9* gene on chromosome 9q34.3, CANDF3 (restricted to nails of the hands and feet) maps to chromosome 11, CANDF4 is caused by mutations in the *CLEC7A* gene on chromosome 12p13.2-p12.3, CANDF5 by mutations in the *IL17RA* gene on chromosome 22q11, and CANDF6 by mutations in the *IL17F* gene on chromosome 6p12.

Familial chronic nail candidiasis has been described with ICAM-1 deficiency with autosomal recessive inheritance (Zuccarello et al. [2002](#)).

### ***Congenital Generalized Fibromatosis***

This is a very rare, probably autosomal recessive, condition characterized by the development of multiple rubbery, firm and fibroblastic tumors of the skin, striated muscle, bones, and viscera from infancy. Multiple subcutaneous nodules proliferate early in life, but tend to regress spontaneously. The visceral involvement may be fatal. Some X-ray features resemble those of Ollier disease (Sty et al. [1996](#)). Autosomal dominant families have been described with the infantile form of this condition (Zand et al. [2004](#)).

### ***Dyskeratosis Congenita***

This is classically an X-linked condition although other inheritance patterns have been described in some families, suggesting genetic heterogeneity, characterized by reticulated hyperpigmentation of the skin, with depigmented spots, nail dystrophy (in 98 % of patients, sometimes apparent at birth), and leukoplakia of the mucous membranes (87 %) with atrophy of the lingual papillae in affected males. Signs of the condition usually develop in the first decade of life, but may not occur until puberty. There may be enamel dystrophy of the teeth. The skin changes are progressive, with development of poikiloderma, telangiectasia, and atrophy. Hypertrophic squamous epithelium occurs in mucous epithelia. Bullous skin eruptions and hyperkeratosis, especially of the palms and soles, may occur, and atrophy of the skin of the palms may lead to loss of dermatoglyphics. Blepharitis, ectropion, and nasolacrimal obstruction may occur, and there are dental caries. Subnormal intelligence is sometimes a feature (42 % of cases). Leukoplakia develops, particularly of the oral mucosa, and also in the rectum and genitourinary tract (Davidson and Connor [1988](#); Fogarty et al. [2003](#)). There is thought to be an immune dysfunction, with reduced cellular immunity and T cell function, leading to opportunistic infections. Complications include pancytopenia (due to bone marrow failure) and squamous and basal cell carcinomas of the skin and mucous membranes, often developing in areas of leukoplakia, after the age of 20 years. Squamous cell carcinoma of the mouth, rectum, cervix, vagina, esophagus, and skin may occur, and there may be multiple primaries. An increased incidence of solid tumors (which can be multiple) has been claimed, with a total incidence of malignancy of 12 % (Kawaguchi et al. [1990](#)). Female carriers are generally normal. Excessive spontaneous chromatid breaks have been reported in some cases of this condition, and an increased X-irradiation-induced chromatid breakage has been demonstrated in fibroblasts. Hematopoietic stem cell transplantation has been tried as therapy in affected patients (Nobili et al. [2002](#)).

Linkage to markers at Xq28(D9S52) was demonstrated, and mutation in the gene encoding dyskerin (*DKC1*) *KKC1* gene is responsible for the condition. Dyskeratin is a protein necessary for the function of telomerase, so the disorder is caused by a defect in the maintenance of telomeres with reduced apoptosis (Kirwan and Dokal 2008). Late-onset cases, or of aplastic anemia, may also be due to mutations in *TERC* (Arngrimsson et al. 1993). Disease anticipation has been shown to be associated with progressive telomere shortening (Montanaro et al. 2003; Shay and Wright 2004; Vuilamy et al. 2004).

## ***Ectodermal Dysplasias***

These conditions comprise a heterogeneous group of congenital diffuse disorders of the epidermis and appendages (Pinheiro and Freire-Maia 1994). Three forms of autosomal dominant ectodermal dysplasia are described, and each of these may predispose to squamous cell carcinoma of the skin and nail beds. The hidrotic type, Clouston syndrome, is characterized by thickened, deformed hypoplastic nails, thin sparse hair, and thick dyskeratotic skin of the palms and soles. Areas of hyperpigmentation occur, especially in skin overlying joints (Escobar et al. 1983). A biochemical defect of keratin may be present, and ultrastructural abnormalities of the hair may be demonstrated. Hypohidrotic ectodermal dysplasia is rare, with hypodontia, hypotrichosis, and variable hypohidrosis. The Rapp–Hodgkin syndrome comprises anhydrotic ectodermal dysplasia and cleft lip and palate. The hair in this condition is short and wiry, the teeth small and conical, and the nails abnormal (Cirillo Silengo et al. 1982). Anhydrotic ectodermal dysplasia is an X-linked recessive condition; the cancer risk is not specifically increased in affected males.

The molecular basis of some of these are being identified – for instance, the X-linked form has been shown to be due to germline mutations in the gene encoding NEMO/IKK gamma, and an autosomal dominant form to germline I Kappa B alpha mutations (Courtois et al. 2003; Lane et al. 2003).

## ***Epidermolysis Bullosa***

This is a heterogeneous group of inherited disorders characterized by extreme skin fragility and recurrent blisters. Classification is based upon the level at which blistering occurs. Superficial blistering occurs in epidermolysis bullosa simplex, with breakdown occurring in the basal cells. This type is often inherited as an autosomal dominant trait and is clinically mild, without scarring, and mucous membranes are spared. Nails may be mildly involved. The autosomal dominant Dowling–Meera form of epidermolysis bullosa simplex can be severe in infancy; the histology of this type is characteristic and can be detected in fetal skin biopsies. In junctional epidermolysis bullosa, the split

occurs in the lamina lucida, causing extensive blistering on the skin and mucosal surfaces. Severe scarring may occur. There are several clinical types of junctional epidermolysis bullosa, all inherited as autosomal recessive traits. Germline mutations in several keratin genes have been found to underlie the different forms of epidermolysis bullosa, the type of mutation correlating with phenotype (Jonkman et al. 2003; Porter and Lane 2003; Uitto et al. 2002; Lin and Carter 1989; Korge and Kreig 1996).

In dystrophic epidermolysis bullosa, blistering occurs in the dermis. Dominant and recessive forms are described, but the severe forms are usually recessively inherited. Bullae develop, particularly on the extremities, leading to severe mitten-like scarring and deformity (mutilans). Gastrointestinal involvement is common, leading to esophageal strictures, erosions, and webs, and life-threatening hemorrhage may occur. Chronic anemia and hypoalbuminemia occur. Dental enamel is defective, and there may be laryngeal involvement.

In epidermolysis bullosa, squamous cell carcinoma may develop in the scars, but this tendency is much more marked in the dystrophic type. These carcinomas may occur at multiple sites, mainly on the limbs (Mallipeddi 2002; Tomita et al. 2003). They arise in young individuals (75 % develop in the 20–40-year age group) and are characteristically well or moderately well differentiated, but aggressive in behavior and metastasize readily (Goldberg et al. 1988). The carcinomas may develop on mucosal surfaces, including esophagus, stomach, bronchus, bladder, and tongue (Tidman 1990). Basal cell carcinomas may also develop in epidermolysis bullosa scars.

Simplex forms of epidermolysis bullosa are caused by mutations in the genes for the basal epidermal keratins *K5* and *K14* (Coulombe et al. 1991), and *K1* and *K10* mutations occur in epidermolytic ichthyosis. Dystrophic epidermolysis bullosa results from mutations in the anchoring fibril collagen gene *COL7A*, whereas the junctional form is due to mutations in *laminin 5* (Eady and Dunnill 1994). Families with autosomal dominant epidermolysis bullosa simplex have shown linkage to the *K14* gene and others to the *K5* gene. Mutations in the *K14* gene have been demonstrated in affected individuals (Bonifas et al. 1991), and a mutation in type VII collagen has been demonstrated in a family with dystrophic epidermolysis bullosa (Bale and DiGiovanna 1997). The genes in which mutations cause epidermolysis bullosa generally encode proteins in or around the hemidesmosome, the sited anchorage of the basal cell to the cell membrane, and the severity of disease determined by the functional position of the affected protein (Fuchs 1996). These genes include *KRT5*, *KRT14*, *PLEC1*, *DST*, *ITGB4*, *ITGA6*, *COL17A1*, *LAMA3*, *LAMB3*, *LAMC2*, and *COL7A1*. Germline mutations in two adjacent genes (*EVER1* and *EVER2*) have been detected in individuals with this condition (Ramos et al. 2002; Tate et al. 2004; Majewski and Jablonska 2004).

### ***KID Syndrome***

This rare condition is characterized by keratitis, ichthyosis, and deafness. It usually occurs as a sporadic condition, but instances of vertical transmission have been



described, indicating autosomal dominant inheritance. There are hyperkeratotic plaques on the skin and reticulated keratosis of the face, with keratoderma. Ichthyosis develops soon after birth, especially over extensor aspects of the skin. Sensorineural deafness is present from birth, and loss of visual acuity develops due to corneal vascularization and opacification. Hair is sparse and the nails may be dystrophic. Recurrent *Candida* infection of the skin occurs in 50 % of cases, although no consistent immunological defect has been demonstrated. Cutaneous infections and abscesses may develop, and multiple squamous cell carcinomas ensue.

Germline mutations in the *GJB2* gene encoding connexin 26 cause this syndrome (Yotsumoto et al. 2003; Janecke et al. 2005).

### ***Multiple Cylindromatosis***

This is an autosomal dominant condition. It is characterized by multiple, smooth, dome-shaped, firm, pink tumors of the head (turban tumors), including syringomas and trichoepitheliomas, and these may be very disfiguring. Basal cell epitheliomas may develop in the lesions, and radiation therapy may exacerbate this tendency.

The tumors are of hairy skin and are not associated with basal or squamous cell carcinomas. The condition has been linked to D16S411 and D16S416 on chromosome 16q12–13.

### ***Flegel Disease (Hyperkeratosis Lenticularis Perstans)***

This is an autosomal dominant condition characterized by punctate keratoses affecting the extensor surfaces of the legs and the dorsa of the feet, with palmar and plantar scaly papules and pits. Keratinosomes may be deficient. There is a risk of squamous and basal cell carcinomas (Li et al. 1997; Miljkovic 2004).

### ***Juvenile Hyaline Fibromatosis***

This is an autosomal recessive condition characterized by multiple subcutaneous scalp. The tumors may be disfiguring, and there is associated gingival hyperplasia. Joint contractures and osteolytic bony lesions often occur. Excision of the tumors may be followed by recurrence (Fayad et al. 1987; Katagiri et al. 1996). The gene for this condition maps to 4q21, and mutations in *CMG2* (capillary morphogenesis gene-2) appear to cause both juvenile hyaline fibrosis and infantile systemic hyalinosis (Rahman et al. 2002; Paller et al. 2003).

### ***Klippel–Trenaunay Syndrome***

This is usually a sporadic condition, characterized by the triad of capillary or cavernous hemangiomas, hemihypertrophy, and varicosities. Additional dermatological features include abnormal pigmentation, papillomas, and varicose ulcers. Arteriovenous aneurysms and lymphatic abnormalities are common (Viljeon 1988).

A de novo translocation t(8;14) (q22.3;q13) has been found in abnormal tissue in this condition (Wang et al. 2001). At least one gene (*RASA1*) in which germline mutations cause this syndrome has been identified (Eerola et al. 2003; Tian 2003), although the latter finding has been recently thrown into doubt (Barker et al. 2006).

### ***Lichen Planus***

This fairly common dermatological condition may predispose to cutaneous malignancy. Familial cases have been described, and in these cases the disease affects younger individuals and is a more widespread eruption (also spreading to involve nails and mucous membranes) than in isolated cases (Sandhu et al. 2003). There may be genetic heterogeneity in etiology in lichen planus, with idiopathic cases of cutaneous lichen planus showing some HLA associations (La Nasa et al. 1995; Sandhu et al. 2003).

### ***Porokeratosis of Mibelli***

This is a rare, autosomal dominant defect of skin keratinization. Centrifugally spreading patches are surrounded by horny ridges, and there is central atrophy. Onset is usually in childhood, and lesions may occur anywhere on the skin, enlarge slowly, and are usually asymptomatic. Squamous cell carcinoma, Bowen's disease, and basal cell carcinoma may develop in the keratoatrophodermic lesions, particularly on the extremities. X-ray treatment may increase the tendency to develop carcinoma. There are other rare forms of porokeratosis: disseminated superficial actinic porokeratosis and porokeratosis plantaris, palmaris, et disseminata, which are also inherited as autosomal dominant conditions predisposing to skin cancer but which occur more in adults and are more likely to be symptomatic. Sporadic cases also occur, and malignancy may be more common in sporadic cases. Males are more often affected than females (Gotz et al. 1999; Goerttler and Jung 1975).

## ***Proteus Syndrome***

This is a very rare condition (named after the Greek god Proteus) and is usually sporadic. Possible transmission of the condition from father to son has been described once (Goodship et al. 1991), but there is considerable debate about this in view of diagnostic pitfalls (Turner 1999). Somatic mosaicism was postulated to explain some cases (Reardon et al. 1996), and this hypothesis has been supported by the identification of somatic mosaic activating mutations in *AKT1* in most if not all cases of well-characterized Proteus syndrome (Lindhurst et al. 2011). Congenital lipomas occur, sometimes with hemangiomatous or lymphangiomatous elements, and progress and are associated with partial or complete hemihypertrophy, asymmetry, and disfiguration. Accelerated growth is seen in the first few years of life. Exostoses of the skull cause macrocephaly and skull asymmetry with frontal bossing. Localized deformities develop, especially of the hands and feet, and hemihypertrophy (segmental to total) is common. Dermatological features include pigmented nevi, diffuse areas of hyperpigmented and depigmented areas of skin, and linear verrucous epidermal nevi, and massive cerebroid gyriform hyperplasia with rugosity of the soles of the feet is a characteristic feature. Bony and adipose overgrowth may lead to bizarre macrodactyly. Subcutaneous hamartomatous tumors, pigmented areas of skin, bony abnormalities, and lung cysts have been described (Nishimura and Koslowski 1990). Intelligence is usually normal. There is a theoretical risk of malignancy in this overgrowth syndrome, and a testicular mesothelioma at the age of 4 years has been described in a severe case (Barker et al. 2001).

Mutations in *PTEN* have been detected in a subset of cases. The second *PTEN* allele has been shown to be inactivated in the abnormal tissue (Zhou et al. 2000, 2001; Smith et al. 2002).

## ***Sclerotylosis (Scleroatrophic and Keratotic Dermatoses of Limbs; Scleroatrophic Syndrome of Huriez)***

This rare autosomal dominant condition is characterized by scleroatrophy of the skin of the hands and feet, hypoplastic nails, and palmoplantar keratoderma. Skin cancer (squamous cell carcinoma) and bowel cancer are said to be common in this condition, and squamous cell carcinomas of the tongue and tonsil also occur. Aggressive squamous cell carcinomas develop on the skin with early onset (third to fourth decade) in about 15 % cases. Linkage has been established with the MN blood group on chromosome 4q28–3. In the scleroatrophic syndrome of Huriez, the histopathologic findings of an almost complete absence of epidermal Langerhans cells in affected skin may explain the susceptibility to squamous cell carcinoma in these lesions (Delaporte et al. 1995; Hamm et al. 1996; Downs and Kennedy 1998; Guerriero et al. 2000; Lee et al. 2000).

### ***Steatocystoma Multiplex***

In this condition, multiple, small, rubbery, elevated, cystic lesions develop, usually in adolescence. The lesions may become infected and this leads to scarring. Autosomal dominant inheritance is the rule. Keratin 17 (*K17*) mutations can cause this condition and PC type 2 (Corden and McLean 1996; Smith et al. 1997).

### ***Syringomas***

A rare condition with multiple facial syringomas, sometimes with neonatal teeth and oligodontia, has been identified as an autosomal dominant condition (Morrison and Young 1996; Metze et al. 2001).

### ***Trichoepithelioma***

This is an autosomal dominant inherited tendency to multiple, small, flesh-colored, translucent tumors from childhood, mainly on the face. There is a risk of basal cell carcinoma developing in the lesions. The condition has been mapped to chromosome 9p21, close to D9S126 (Harada et al. 1996; Clarke et al. 2002). The condition is caused by mutations in the *CYLD* gene, thus allelic with Brooke–Spiegler syndrome (Saggar et al. 2008). Brooke–Spiegler (p. 192) syndrome is an autosomal dominant syndrome characterized by multiple cylindromas and trichoepitheliomas.

### ***Tylosis***

Tylosis, or focal epidermolytic palmoplantar keratoderma occurring after infancy, is associated with early-onset squamous cell carcinoma of the esophagus in three families. The tylosis is characterized by abnormal thickening of the palmoplantar skin. Neonatal onset of palmoplantar keratosis is a different disorder and not associated with esophageal cancer. The genetic locus for the tylosis esophageal cancer (*TOC*) gene has been localized to 17q25 (Langan et al. 2004) and the responsible gene has recently been identified (see section on Esophageal Cancer).

### ***Lichen Sclerosis Et Atrophicus***

This dermatological disorder is much more common in females than in males (10:1), has a predilection for the vulva, particularly in postmenopausal women, and is the most commonly encountered vulvar dystrophy. Extragenital lesions are most common on the trunk, arms, neck, and face. The lesions are greyish, polygonal, flat papules, which may coalesce into plaques which atrophy. The vulvar lesions predispose to carcinoma of the vulva, with a reported incidence of up to 10 % of affected adult women. The lesions show elevated p53 levels and 17p loss of heterozygosity (LOH). Several cases of familial lichen sclerosis with more than one affected generation have been described, including premenopausal women and children, but these are very rare (Shirer and Ray 1987; Carlson et al. 1998).

### ***Mast Cell Disease***

This includes a wide spectrum of clinical entities, with urticaria pigmentosa with or without systemic lesions, and may rarely be associated with malignant mast cell leukemia. Symmetrical hyperpigmented macules or papules may develop from infancy, most commonly on the trunk; they urticate on mild trauma. Vesiculation, erythema, and telangiectasia may develop. Pruritus is common and may be accompanied by flushing, tachycardia, and malaise. Familial instances with autosomal dominant trait inheritance have been described (Shaw 1968). A somatic point mutation in *KIT* may be detected in peripheral blood mononuclear cells in patients with mastocytosis with an associated hematological disorder (Nagata et al. 1995; Fritsch-Polanz et al. 2001; Ferger et al. 2002; Chang et al. 2001). *TET2* mutations have been found in the bone marrow of affected cases (Tefferi et al. 2009).

### ***Multiple Cutaneous Leiomyomas***

This is an autosomal dominant condition in which many small smooth muscle tumors develop in the skin. These tumors appear as single or multiple small, firm, painful dermal nodules, fixed to the skin, especially noted on the limbs, trunk, and face, and develop more often in the third decade of life, although they can occur in childhood. Uterine myomas may be associated; 54 % of affected females in one family described in the literature had uterine myomas. These

may rarely develop into leiomyosarcomas (Berendes et al. 1971), and there is also an increased risk of type II papillary renal cancer or renal cancer with collecting duct morphology. Affected individuals have reduced fumarate hydratase (FH) activity in lymphoblastoid cells. In the majority of cases, the condition is due to germline heterozygous mutations in the *FH* gene, a component of the tricarboxylic acid cycle (Martinez-Mir et al. 2003; Tomlinson et al. 2002). Homozygotes (or compound heterozygotes for FH mutations) cause the fumarase metabolic deficiency syndrome characterized by developmental delay and death in the first decade (Tomlinson et al. 2002; Alam et al. 2003). However, not all mutation carrier parents of children with FH deficiency have a predisposition to leiomyomata.

Screening affected individuals should include regular abdominal imaging for renal abnormalities (MRI scans are preferred as tumours can be isoechogenic) (Garman et al. 2003; Wei et al. 2006) which should be initiated early, because cases of renal cancer have been described in individuals as young as 11y with germline FH mutations (Alrashdi et al. 2010) (see p. 140).

### ***Multiple Lipomatosis: Familial***

This rare autosomal dominant condition is characterized by the development of multiple, encapsulated, subcutaneous, non-tender, smooth lipomas on the forearms, trunk, thighs, and arms. The lipomas are often symmetric, usually begin in early adulthood, and grow to a certain size and then stabilize; regression is rare, as is malignant degeneration. The distribution of the lipomas may follow that of the peripheral nerves (Leffell and Braverman 1986). In one family the condition was linked to an *RBI* gene mutation with low-penetrance retinoblastoma susceptibility (Genuardi et al. 2001). Germline mutations in the *HMG2* gene may be responsible for dominant familial multiple lipomatosis, and that somatic mutations in this gene may be responsible for encephalocutaneous lipomatosis (Prontera et al. 2009).

### ***Multiple Lipomatosis: Symmetric***

This is a separate condition, predominantly occurring in adult males, and autosomal inheritance has been suggested. The primary defect is thought to be in adrenergic-stimulated lipolysis. Clinically, lipomatous masses develop in a symmetric distribution at the back of the neck and shoulders, the breast areas, abdomen, and pubic regions. There may be atrophy of uninvolved fat. Visceral lipomatosis can be life-threatening. Autonomic and peripheral neuropathy is

associated, and alcoholism is thought to precipitate its development in many cases. The condition is probably heterogeneous and may not be genetic, but may be confused with multiple lipomatosis. Autosomal dominant inheritance of multiple familial lipomatosis with polyneuropathy has been described (Wilson and Boland 1994; Stoll et al. 1996; Nisoli et al. 2002), and mutations in the mitochondrial genome, possibly resulting in faulty noradrenergic modulation of proliferation and differentiation of brown fat cells (Gamez et al. 1998; Nisoli et al. 2002; Enzi et al. 2002).

### ***NAME Syndrome: Carney Complex***

Carney complex is an autosomal dominant multiple endocrine neoplasia and lentiginosis syndrome characterized by spotty skin pigmentation; cardiac, skin, and breast myxomas; and a variety of endocrine tumors. The skin features include common and blue nevi and psammomatous melanotic schwannomas. Endocrine overactivity occurs. Pituitary tumors, adrenal cortical rest tumors, pheochromocytoma, Leydig cell tumors, large cell calcifying Sertoli cell tumor of the testis, schwannomas, and myxoid breast fibroadenomas and ductal adenomas have all been described in this condition (Carney 1995). The most common manifestation is an ACTH-independent Cushing's syndrome due to primary pigmented nodular adrenocortical disease (PPNAD).

The condition is genetically heterogeneous. Mutations in the gene encoding the protein kinase A type 1- $\alpha$  regulatory subunit (*PRKARIA*) on chromosome 17q have been identified in about three quarters of affected individuals (Kirschner et al. 2000a, b; Veugelers et al. 2004); other families show linkage to chromosome 2p16 (Stratakis et al. 1996), and chromosome 2 abnormalities have been described in the tumors (Matyakhina et al. 2003) (see p. 228).

This syndrome is distinct from the Carney triad, an association between stromal gastric sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney 1999).

### ***Pachyonychia Congenita***

This rare autosomal dominant condition is characterized by thickened nails (which are very difficult to cut), with yellow discoloration, follicular keratosis in 59 %, plantar keratosis in 72 %, and leukokeratosis in 57 % of cases. The nail abnormalities may be seen soon after birth, and paronychia inflammation occurs. Subcutaneous hamartomatous cysts, bullae, ichthyosis, and hyperkeratosis may develop. Blistering may occur over pressure areas, and there may be



deafness, hair and dental abnormalities, hyperhidrosis, and corneal opacification. Oral leukoplakia is seen. Malignant changes may occur in the oral lesions, in cysts, or at sites of chronic plantar ulcerations, so that areas of chronic ulceration or bullous formation should be observed for the possible development of malignancy (Su et al. 1990). Steatocystoma multiplex is considered to be the same condition. Germline mutations in the K17 gene may underlie certain types of this condition (Smith et al. 1997); others may be due to missense mutations in keratin 17 (Smith et al. 1997; Feinstein et al. 1988; Hodes and Norins 1977; Stieglitz and Centerwall 1983).

Pachyonychia congenita (PC) types 1 and 2 are described. These are similar but type 1 gets oral leukokeratoses, whereas type 2 has premature dentition and multiple sebaceous cysts. Mutations in the keratin 17 (*K17*) gene can cause PC type 2 or steatocystoma multiplex PC types 1 and 2 with hypertrophic nail dystrophy, focal keratoderma, and sebaceous cysts (Corello et al. 1998). PC type 1 is due to K6a and K16 mutations (Swenssen 1999).

### ***Palmar Keratoses***

It has been claimed that palmar and plantar keratoses are more common in individuals with bladder and lung cancer, occurring in 70–90 % of cases and in only 36 % of controls, but it is difficult to assess the significance of this finding since it is based on only a few studies (Cuzick et al. 1984). Keratin gene or connexin abnormalities may underlie this group of conditions (Bale and DiGiovanna 1997; Kelsell et al. 2000; Kimyai-Asadi et al. 2002; Radi et al. 2005).

There are many subtypes, including palmoplantar keratoderma, the Clarke–Howel–Evans syndrome (see Esophageal Cancer) (Malde, Meleda, Smith 2003). Mutations of the KRT1 and KRT9 genes may cause the epidermolytic form of PPK. Both epidermolytic and nonepidermolytic forms of palmoplantar keratoderma have been observed with various mutations in the KRT1 gene (Chiu et al. 2007).

### ***Pilomatrixoma (Benign Calcifying Epithelioma of Malherbe)***

Pilomatrixomas appear in young adults, most commonly on the arms, face, and neck, as asymptomatic, firm, lobular, bluish nodules, which may be painful and occasionally inflamed. They are usually sporadic but have rarely been found to occur in families. They occur in both sexes, possibly with autosomal dominant inheritance. Multiple calcifying epitheliomas have been reported in association with myotonic dystrophy (Harper 1972; Hubbard and Whittaker 2004) and with Rubinstein–Taybi syndrome (Masuno et al. 1998). Activating mutations in *CTNNB1* are detected in a high proportion of tumors (Chan et al. 1999).

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## Chapter 11

# Inherited Cancer-Predisposing Syndromes

### Ataxia Telangiectasia (OMIM 208900)

This autosomal recessive disorder, with a birth incidence of about 1 in 300,000, is characterized by the development of cerebellar ataxia in the first decade, along with choreoathetosis, dysarthria, and abnormalities of ocular movements. Mental retardation is not usually a feature. The neurological features are progressive, leading to confinement to a wheelchair in the second decade of life. Oculocutaneous telangiectasia develops in childhood (often after ataxia is apparent) and then spreads to involve other exposed cutaneous areas. Vitiligo, café-au-lait spots, and macular hyperpigmentation may occur. The development of acanthosis nigricans is associated with the development of neoplasia. An immune deficiency occurs, with disordered B cell and T helper cell function, thymic hypoplasia, reduced levels of IgA (70 %) and IgE (80 %), and reduced T cells. Frequent bacterial (pulmonary or sinus) infections occur secondary to immunodeficiency. The serum alpha-fetoprotein is consistently elevated. There is an inconsistently increased incidence of spontaneous structural chromosomal aberrations (30–50-fold) (chromatid gaps, breaks and interchanges, and telomere fusions) in cultured white cells and fibroblasts, and this is markedly increased by exposure to X-radiation and radiomimetic agents. Peripheral blood lymphocytes may show abnormal clones of cells with a stable cytogenetic rearrangement, usually involving chromosome 14, particularly involving the T cell receptor genes on 14q11, 7q14, and 7q35. Clones of cells with these translocations may develop into T cell promyelocytic leukemia. Other translocations involve the immunoglobulin genes in B lymphocytes. In vivo sensitivity to X-rays is also observed. Recombination is increased by a factor of 30–200 (Tomanin et al. 1989; Peterson et al. 1992; Viniou et al. 2001; Sun et al. 2002).

There is a 30–40 % risk of malignancy developing, most frequently Hodgkin and non-Hodgkin lymphoma (60 %) and lymphoblastic T cell leukemia (27 %) (Johnson 1989). The lymphoreticular neoplasms develop before the age of 16 years, and epithelial carcinomas (including medulloblastomas; gastric, basal cell, hepatocellular, parotid, laryngeal, skin, and breast carcinomas; uterine leiomyomas; and ovarian

dysgerminoma) may develop in patients surviving longer (Spector et al. 1982). Severe reactions have been described to standard doses of radiotherapy in this condition.

The *ATM* gene was cloned in 1995 (Savitsky et al. 1995). Its product, ATM, has a central role in orchestrating the response to double-strand breaks. It is a serine/threonine kinase that mediates checkpoint regulation and homologous repair by phosphorylating a number of proteins; without it, cells display aberrant cell-cycle progression and increased chromosomal breakage, especially when exposed to ionizing radiation. McConville et al. (1996) and others have reported families with a milder clinical and cellular phenotype due to certain ataxia-telangiectasia mutations (Sariozzi et al. 2002; Chessa 2003) causing reduced ATM function. The *ATM* carrier frequency is estimated to be about 1 %, and early studies showed that these heterozygotes have an increased risk of cancer, particularly breast cancer (Morrell et al. 1990). This was supported by studies conducted after the gene was identified (Athma et al. 1996; Thomson et al. 2005). These epidemiological studies were confirmed directly when Renwick et al. identified 12 deleterious mutations in 443 affected cases compared to 2 out of 521 controls resulting in an estimated relative risk of 2.37 (Renwick et al. 2006). One limitation of the study however was that the significance of 35 of 37 missense mutations identified could not be determined. To try to solve this problem, Tavtigian et al. used an *in silico* approach to test the hypothesis that missense mutations in evolutionary conserved residues would be more common among breast cancer patients than in controls. Suggestive of a dominant-negative model, they found that missense mutations ranked highly deleterious were associated with an even greater risk of breast cancer than truncation or splice site mutations, demonstrating that not all variants have equal risk predisposition (Tavtigian et al. 2009; Thorensten et al. 2003), but this remains controversial.

## Ataxia-Telangiectasia-Like Disorder (ATLD) (OMIM 604391)

A small proportion of “AT” cases have mutations in the *MRE11* gene rather than *ATM*, causing a disorder known as ATLD. The lymphocytes of such patients show increased levels of translocations involving immune system genes, and chromosomal radiosensitivity is seen, but B lymphocytes may not be affected and the cancer risk is less (Stewart et al. 1999; Duker 2002; De la Torre et al. 2003). *MRE11* is part of the MRN (*MRE11*–*RAD50*–*NBN*) complex. MRN appears to be the primary sensor of DNA damage, signaling ATM to sites of double-strand breaks to initiate the DNA damage response (Lavin 2007). It also has important downstream functions that include tethering and processing the two broken ends of the DNA strand to generate 3′ overhangs for either non-homologous end-joining or homologous repair. Its role in maintaining genome integrity is underscored by chromosome instability and cell-cycle checkpoint defects common to all patients with recessive loss of any one of these components. Heterozygous mutations in *NBN* and *RAD50* (Heikkinen et al. 2006) have been associated with an increased risk for breast cancer (mainly in countries where founder mutations in these genes have been identified). Rare germline mutations in *MRE11* have also been proposed to be breast cancer alleles – in one study of eight tumors showing

concomitant reduction/loss of all three MRN-complex proteins, mutation analysis revealed two germline mutations in *MRE11*: a missense mutation Arg202Gly and a truncating mutation Arg633X (Bartkova et al. 2008). This study remains to be verified in large case-control studies. One likely truncating mutation in *MRE11A* was identified in 360 women with ovarian carcinoma (Walsh et al. 2011).

## **Bannayan–Riley–Ruvalcaba Syndrome (Bannayan–Zonana Syndrome, Ruvalcaba–Riley–Smith Syndrome)**

Bannayan–Riley–Ruvalcaba syndrome (BRRS, MIM 153480), a rare autosomal dominant congenital disorder, is characterized by macrocephaly, lipomatosis, hemangiomas, and speckled penis (Gorlin et al. 1992). Other features include Hashimoto thyroiditis, gastrointestinal (GI) hamartomatous polyposis most likely not associated with GI malignancy, hypotonia, and variable mental retardation and psychomotor delay. While a lipid storage myopathy is still considered a component to BRRS, its original etiology, long-chain acyl-coA dehydrogenase (LCHAD) deficiency, has been questioned.

Germline *PTEN* mutations were originally found in two classic BRRS families (Marsh et al. 1997), and thus, a subset of BRRS is allelic to Cowden syndrome (see p. 233) (Marsh et al. 1999). Subsequently, 60 % of a series of BRRS probands were found to have germline *PTEN* mutations (Marsh et al. 1999). Of those that were mutation negative after PCR-based mutational analysis of exons 1–9 and flanking intronic regions, 10 % have been found to carry large deletions including or encompassing *PTEN* (Zhou et al. 2003a, b). Genotype–phenotype association analysis reveals that BRRS carrying germline *PTEN* mutations were at increased risk of neoplasia, especially malignant breast disease, and lipomatosis compared to those without *PTEN* mutations (Marsh et al. 1999).

Traditionally, medical management of BRRS has been symptomatic. However, given the genotype–phenotype association and that a subset of BRRS is allelic to Cowden syndrome, individuals with BRRS, especially those found to have germline *PTEN* mutations, should undergo similar surveillance and management to individuals with Cowden syndrome (p. 233). Because thyroid cancers can occur even in the teens in BRRS, it would be prudent to begin annual comprehensive physical examinations, paying particular attention to the neck, in the early teens.

## **Beckwith–Wiedemann Syndrome (EMG Syndrome and IGF2 Overgrowth Disorder) (OMIM 130650)**

This syndrome, with an estimated incidence of 1 in 14,000, is characterized by major (pre- and/or postnatal overgrowth, anterior abdominal wall defects (diastasis recti, umbilical hernia, or exomphalos), and macroglossia) and minor features

(earlobe grooves or helical rim pits, facial nevus flammeus, visceromegaly (liver, kidney, spleen), neonatal hypoglycemia, hemihypertrophy, renal anomalies, cryptorchidism, and, infrequently, cardiac defects). In addition embryonal tumors occur in ~8 % of patients (though the risk depends on the underlying specific genetic/epigenetic abnormality) (Wiedemann et al. 1983; Hatada et al. 1996; Koufos et al. 1989).

There are no consensus clinical diagnostic criteria for Beckwith–Wiedemann syndrome (BWS). Strict diagnostic criteria were suggested by Elliott and Maher (1994) that required the presence of (1) three major features or (2) two major features plus three minor features (from ear creases or pits, hypoglycemia, nephromegaly, or hemihypertrophy), but less strict diagnostic criteria have also been proposed, for example, at least two from (a) positive family history; (b) macrosomia (height and weight >97 percentile); (c) anterior linear earlobe creases/posterior helical ear pits; (d) macroglossia; (e) exomphalos/umbilical hernia; (f) visceromegaly involving one or more intra-abdominal organs including liver, spleen, kidneys, adrenal glands, and pancreas; (g) embryonal tumor (e.g., Wilms tumor, hepatoblastoma, rhabdomyosarcoma) in childhood; (h) hemihypertrophy; (i) adrenocortical cytomegaly; (j) renal abnormalities including structural abnormalities, nephromegaly, and nephrocalcinosis; and (k) cleft palate (rare) and one from (a) polyhydramnios, (b) neonatal hypoglycemia, (c) facial nevus flammeus, (d) hemangioma, (e) characteristic facies including midfacial hypoplasia and infraorbital creases, (f) cardiomegaly/structural cardiac anomalies/rarely cardiomyopathy, and (g) diastasis recti and advanced bone age (<http://www.geneclinics.org>). However, molecular genetic testing can diagnose most cases (Cooper et al. 2005).

The characteristic craniofacial dysmorphological features of Beckwith–Wiedemann syndrome (BWS) are most apparent before the age of 3 years, and after the age of 5 years, there are often only minor dysmorphisms. The differential diagnosis of BWS includes Perlman syndrome, Simpson–Golabi–Behmel syndrome, and other overgrowth disorders, such as Weaver or Sotos syndrome.

The genetics of BWS are complex (Choufani et al. 2010; Lim and Maher 2010). Most cases are sporadic but ~15 % of cases are familial. The inheritance pattern of familial cases is dependent on the nature of the genetic cause (see later), but in most cases it will be autosomal dominant trait with parent-of-origin effects such that the penetrance is more complete when the mother is the transmitting parent, and examples of transmitting males with affected children are rare. As there is wide variation in expression of the disease and the features of BWS tend to become less apparent with age, it is likely that some familial cases of BWS are misdiagnosed clinically as sporadic cases because minor manifestations in relatives are overlooked. Though characterization of the molecular pathology in an individual case may indicate whether the disorder is likely to be sporadic or familial, careful examination of close relatives (particularly the mother) should be performed.

An association between twinning and BWS has been recognized. Thus a greater than expected number of twins have been described among BWS children, and these are usually female monozygotic twins that are discordant for BWS (Blik et al. 2009).

The parent-of-origin effects on the penetrance and expression of familial BWS suggested a genomic imprinting disorder, and molecular tests (see below) have confirmed that BWS results from abnormal function/expression of imprinted genes (in particular the paternally expressed growth factor *IGF2* and the maternally expressed growth suppressor *CDKN1C*) contained within a cluster of imprinted genes at chromosome 11p15.5. Interestingly, the frequency of BWS and some other genomic imprinting disorders appears to be increased in children conceived by assisted reproductive technologies (both ICSI and in vitro fertilization) (DeBaun et al. 2003; Maher et al. 2003; Lim et al. 2009). Though the relative risk of having a child with BWS is increased after BWS (probably up to tenfold), the absolute risk appears to be small (less than 1 in 1,000).

BWS may result from chromosomal rearrangements (duplications or translocations/inversions of distal chromosome 11p), uniparental disomy of 11p15.5, mutations, or epimutations directly involving the two 11p15.5 imprinting control regions (IC1 and IC2). In addition germline mutations in *CDKN1C* or inactivation of *NLRP2* in the mother can cause familial BWS (Cooper et al. 2005; Choufani et al. 2010; Lim and Maher 2010).

Chromosome 11p15.5 was first implicated in BWS by the finding of paternally derived duplications of 11p15.5 in BWS patients. Subsequently maternally inherited balanced rearrangements of 11p15 were also demonstrated to be associated with BWS. It is estimated that up to 3 % of BWS patients have a cytogenetically visible chromosome duplication or rearrangement. Chromosome 11 paternal uniparental disomy is found in approximately 20 % of sporadic cases of BWS. Typically uniparental disomy in BWS is mosaic paternal isodisomy, and although the disomic region always includes the imprinted gene cluster at 11p15.5, involvement of more centromeric regions of 11p and of 11q is variable. A few patients diagnosed with BWS have been demonstrated to have whole genome paternal uniparental disomy, and these cases appear to have an increased risk of neoplasia (e.g., pheochromocytoma, hepatoblastoma) (Romanelli et al. 2011).

Epigenetic errors at two putative imprinting control regions within 11p15.5 (IC1 and IC2) have also been implicated in BWS. Thus, 5 % of BWS patients have an imprinting defect at the distal imprinting center (IC1) such that the maternal *IGF2* and *H19* alleles display a paternal epigenotype (hypermethylation and silencing of *H19* and biallelic *IGF2* expression). In up to 50 % of cases, there is loss of paternal methylation at IC2 (KvDMR1) that is associated with silencing of *CDKN1C* expression and variable loss of imprinting (biallelic expression) of *IGF2*. Cases associated with assisted reproductive technologies and those that occur in twins are very likely to have loss of paternal methylation at IC2 (KvDMR1). In general the risk of recurrence after a child with an imprinting center epimutations is very low if an *in cis* duplication or deletion has been excluded. However in rare cases, an epimutation may result as an *in trans* effect of maternal homozygosity for a *NALP2* mutation (Meyer et al. 2009).

Germline inactivating *CDKN1C* mutations occur in about half of familial cases and 5 % of sporadic cases (Lam et al. 1999). *CDKN1C* is expressed from the maternal allele (though there is a small level of paternal allele expression), and so a paternally transmitted mutation has minimal effect of the children who inherit the

mutation. In contrast a maternally inherited *CDKN1C* mutation will cause BWS (Maher and Reik 2000).

Genotype–phenotype correlations have been described for hemihypertrophy and exomphalos. Most cases with hemihypertrophy have mosaic uniparental disomy. There is a high incidence of exomphalos in patients with *CDKN1C* mutations and IC2 imprinting center defects, but exomphalos is infrequent in patients with uniparental disomy or IC1 imprinting center defects. In addition to patients with classical BWS, Morison et al. (1996) reported that some patients with overgrowth and nephromegaly or Wilms tumor may have biallelic *IGF2* expression, and they coined the term “IGF2 overgrowth disorder” to describe these patients (Gicquel et al. 2003).

Patients with BWS have an increased risk of neoplasia. Wiedemann (1983) reviewed 388 children with BWS and found 29 children (7.5 %) with 32 tumors. Most tumors (26/29) were intra-abdominal (including 14 Wilms tumor, 5 adrenal carcinomas, and 2 hepatoblastomas). Most tumors occur before the age of 5 years. A clinical association between hemihypertrophy and neoplasia in BWS was noted, and among patients with BWS, the risk of Wilms tumor is highest in those with uniparental disomy and IC1 imprinting center defect, and the risk of Wilms tumor appears minimal in those with IC2 imprinting center defects and *CDKN1C* mutations (Engel et al. 2000; Weksberg et al. 2003; DeBaun et al. 2002; Cooper et al. 2005). Thus, in one study the risk of embryonal tumors was 9 % at age of 5 years in all cases but 24 % in those with uniparental disomy (Cooper et al. 2005). As the risk of Wilms tumor appears to be very low in children with IC2 imprinting defects and *CDKN1C* mutations, there is no indication for Wilms tumor surveillance (e.g., 3-monthly renal ultrasonography) in such cases. However, hepatoblastoma can occur in children with IC2 defects, and though the absolute risk of hepatoblastoma is low and the utility of screening for hepatoblastoma alone is unproven, some parents may request surveillance by serum alpha-fetoprotein measurements.

## Birt–Hogg–Dubé Syndrome (OMIM135150)

Following the description of familial renal oncocytoma (Weirich et al. 1998), it was reported that some familial renal oncocytoma kindreds contained affected individuals with rare hamartomatous tumors of the hair follicle known as fibrofolliculoma (Toro et al. 1999). Fibrofolliculomas are a characteristic feature of the dominantly inherited multisystem familial cancer syndrome Birt–Hogg–Dubé syndrome (Birt et al. 1977). Benign whitish-grey papular skin tumors develop on the face and upper body in the third decade, and histological examination reveals fibrofolliculomas or trichodiscomas (Birt et al. 1977; Rongioletti et al. 1989). Additional features include lipomas and cystic lung lesions and pneumothorax. In some reports, colonic polypsis is described (the combination of skin fibrofolliculomas and colorectal polyps described by Hornstein and Knickenberg (1975) is now considered to be BHD syndrome), and an increased risk of colorectal cancer has been reported in some studies but not in others (Zbar et al. 2002; Nahorski et al. 2010). Lifetime risk of renal cell

carcinoma in BHD is about 30 % with a mean age of diagnosis of ~50 years (Menko et al. 2009). A variety of histopathological subtypes of RCC have been described in Birt–Hogg–Dubé syndrome; a hybrid oncocytoma/chromophobe is characteristic, but other types including chromophobe and clear cell (conventional) RCC may occur (Pavlovich et al. 2002; Menko et al. 2009). Germline BHD gene (*FLCN*) mutations may be detected in ~5 % of patients with features of non-syndromic inherited RCC and also in kindreds with familial pneumothorax (Woodward et al. 2008; Graham et al. 2005).

The suggested diagnostic criteria for BHD syndrome require the presence of one major (at least 5 fibrofolliculomas–trichodiscomas, at least one histologically confirmed, of adult onset or a pathogenic germline mutation) or two minor criteria (multiple lung cysts (bilateral basal lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax) or renal cancer: early-onset (<50 years) and/or multifocal/bilateral renal cancer and/or renal cancer of mixed chromophobe/oncocytic histology) or a first-degree relative with BHD syndrome.

The *BHD* gene maps to 17p11.2 and encodes a 64-kDa protein (Nickerson et al. 2002). A frameshift mutation hotspot in a mononucleotide tract ( $C_8$ ) in exon 11 accounts for ~50 % of mutations and most mutations are protein truncating (see <http://www.lovd.nl/flcn>). Molecular genetic diagnostic testing diagnosis should consist of sequence analysis and analysis (e.g., MLPA) for exonic deletions and amplifications. Two naturally occurring animal models of Birt–Hogg–Dubé syndrome, in the German shepherd dog and rat, have been described (Jonasdottir et al. 2000; Okimoto et al. 2004). The folliculin protein may negatively regulate AMPK and mTOR-related pathways, though the effects on mTOR may be context dependent and folliculin function has not yet been fully elucidated (Menko et al. 2009).

Surveillance for renal tumors is recommended by annual MRI scan of the kidney starting at the age of 20 years. As in von Hippel–Lindau disease, renal tumors <3 cm can be monitored and nephron-sparing surgery performed when they reach 3 cm. In view of the risk of pneumothorax, caution should be exercised for circumstances which might precipitate pneumothorax, such as general anesthesia. Individuals with BHD syndrome who develop pneumothorax will have lung cysts (usually basal), and so a lung CT scan may predict risk of pneumothorax. Fibrofolliculomas are benign and do not need treatment other than for cosmetic reasons. The role of colonoscopy in BHD syndrome is uncertain, but in families in which colorectal cancer has occurred, 3-yearly colonoscopy from age 45 years is indicated.

## Blackfan–Diamond Syndrome (OMIM 105650)

This rare disorder (>1 in 250,000 births) is characterized by congenital hypoplastic anemia with normal leucocyte and platelet counts. Approximately 10–25 % are familial with the majority sporadic. Approximately 30–40 % have other congenital anomalies such as upper limb and craniofacial anomalies. There is an increased risk of leukemia (Alter 1987). Gustavsson et al. (1997) estimated that 10–20 % of cases



followed a recessive or dominant inheritance pattern, and they mapped a gene to chromosome 19q13 for both recessive and dominant forms. Subsequently Draptchinskaia et al. (1999) demonstrated germline mutations in the *RPS19* gene in Blackfan–Diamond anemia (DBA, MIM105650). Overall about 25 % of DBA patients have *RPS19* mutations, but multiple loci have now been identified (Gazda et al. 2001; Boria et al. 2010). Interestingly, there are at least ten forms of DBA, all of which are due to germline mutations in genes responsible for ribosome synthesis. DBA is a consequence of defective ribosome biogenesis and defective protein translation (Boria et al. 2010). While germline mutations in *RPL5* seemed to confer increased risk of thumb, but not craniofacial anomalies, none of those with *RPL11* mutations had such anomalies (Gazda et al. 2008).

## Bloom Syndrome (OMIM 210900)

This rare autosomal recessive condition is much more common in Ashkenazi Jews than in other ethnic groups. It is characterized by low birth weight, growth deficiency, and a sunlight-sensitive erythematous and telangiectatic rash, especially on the face from the first year of life. Sun exposure accentuates these changes, and may induce bullae, with bleeding and crusting on the face (especially the lips and eyelids). The nose is prominent in a long thin face, and there is clinodactyly. Spotty hypopigmentation and hyperpigmentation may be seen on the skin, and also “twin spots,” which may be due to somatic recombination (Bloom 1966). Adult height is usually less than 150 cm. Intelligence is normal. There is a severe immune defect with reduced gammaglobulin (IgA and IgM) levels, leading to a high incidence of chronic severe infections of the respiratory and GI tract. About 20 % of patients with Bloom syndrome develop neoplasms, half of these before the age of 20 years, and tumors may be multiple. Neoplasms are predominantly lymphatic and non-lymphatic leukemia, lymphoma, and carcinomas of the mouth, stomach, esophagus, colon, cervix, and larynx. Early cervical screening should be offered to affected women. Screening for other cancers may be problematic, although regular oral examinations by a dental surgeon and colonoscopy are also probably worthwhile. Myeloid leukemia and myelodysplastic syndrome have been reported, often with monosomy for chromosome 7 (Ellis and German 1996; Aktas et al. 2000; Poppe et al. 2001). Wilms tumor has been described in four children with Bloom syndrome, and one of these four children had a sib who developed a hepatocellular carcinoma at age of 15 years (Cairney et al. 1987; Jain et al. 2001).

Few patients survive into adulthood, but in those that do, colorectal cancer has been reported. In one case, this occurred in the context of ulcerative colitis (Wang et al. 1999), whereas in other case, an attenuated familial adenomatous polyposis (FAP) phenotype was observed (Lowy et al. 2001). Interestingly, a mucinous (i.e., hereditary non-polyposis colorectal cancer-like) transverse colon cancer, with normal p53 expression, has been reported in a 16-year-old with Bloom syndrome. These observation led investigators to study the gene, *BLM*, identified by Ellis et al.

(1995) in individuals from the population with colorectal cancer. One mutation, *BLM*: 2281del6ins7 is seen in approximately 1 in 110 Ashkenazi Jews, so this population was studied in detail. Overall, 1 in 54 Jews with colorectal cancer carried this allele, whereas the allele was seen in 1 in 118 controls (odds ratio, 2.76; 95 % CI, 1.4–5.5) (Gruber et al. 2002). This finding was supported by data showing that mice heterozygous for *Blm* developed twice the number of intestinal tumors when crossed with mice carrying a mutation of the *Apc* tumor suppressor gene (Goss et al. 2002). Somatic mutations in length repeats within *BLM* are also quite frequent in sporadic colorectal cancer (Calin et al. 1998) and, interestingly, tend to be associated with mucinous colorectal cancers (Calin et al. 2000). Knocking out *BLM* in karyotypically stable colorectal cancer cell lines results in increased sister chromatid exchange and homologous recombination (but without gross chromosomal rearrangements) (Traverso et al. 2003). Finally, in a murine model, chromosomal instability and tumor predisposition seem to correlate inversely with *BLM* protein levels (McDaniel et al. 2003). Taken together, these findings suggest that homozygous individuals are at considerably increased risk for colorectal cancer and that heterozygosity for *BLM* can be added to the I1307K *APC* allele as a genetic risk factor for colorectal cancer in the Jewish population, I1307K, however, is at least 6 times as prevalent as *BLM*<sup>Ash</sup>, and thus the clinical significance of the latter allele is very limited. Another possible founder mutation has been reported in Japan: *BLM*: 631delCAA (Kaneko et al. 2004), and studies of this allele in colorectal cancer in Japan would be of interest.

At the nuclear level, an elevated frequency of chromosomal breaks is observed, with an increase in sister chromatid exchanges, and an abnormal profile of DNA replication intermediates is reported in this condition (Lonn et al. 1990). The exact mechanism by which *BLM* maintains replication fidelity is debated. In a mouse model of Bloom syndrome, viable mice were prone to cancers at many sites, and cell lines showed elevated levels of mitotic recombination (and therefore loss of heterozygosity) (Luo et al. 2000). These data were supported by results in human cancer cells, as discussed above (Traverso et al. 2003).

There is a registry for cases of Bloom syndrome to help affected individuals and their families and to assist in the assessment of the natural history of the disease. The registry can be contacted at <http://med.cornell.edu/bsr/>. According to this website, as of 2009, there were 265 persons with Bloom syndrome registered.

## Blue Rubber Bleb Nevus Syndrome (OMIM112200)

This may occur as an autosomal dominant trait, but is usually sporadic and of unknown etiology. Multiple vascular nipple-like lesions occur, especially on the trunk and upper arms and mucous membranes, and intestinal, hepatic, and pulmonary angiomas may develop (Dobru et al. 2004). Bleeding from these lesions can lead to anemia (Fukhro et al. 2002). Central nervous system (CNS) hemangioma and cerebellar medulloblastoma may also occur (Satya-Murti et al. 1986; Kim

2000). It has been suggested that this syndrome is a variant of familial (autosomal dominant) venous malformations which has been mapped to chromosome 9p by linkage studies in two large kindreds (Gallione et al. 1995), and germline mutations in the endothelial cell-specific receptor tyrosine kinase gene *TIE2* (*TEK*) have been detected in some families; somatic mutations in the same gene can be demonstrated in sporadic cases (Nobuhara et al. 2006; Limaye et al. 2009).

### **Carney–Stratakis Syndrome (Carney Dyad; Dyad of Parangangliomas and Stromal Tumors) (OMIM606864)**

Carney–Stratakis syndrome (CSS) or Carney dyad should not be confused with the more classic Carney triad, the latter of which comprises paragangliomas (PGL), gastrointestinal stromal tumors (GIST), and pulmonary chondromas. In contrast to Carney triad which occurs sporadically, CSS is an autosomal dominant condition characterized by PGL or pheochromocytoma and GIST (Stratakis and Carney 2009). Recently, germline heterozygous mutations in *SDHB*, *SDHC*, or *SDHD*, encoding three of the four subunits of succinate dehydrogenase (mitochondrial complex II), were found in individuals and families with CSS (McWhinney et al. 2007; Pasini et al. 2008). In this initial series, 8 of 11 CSS individuals harbored *SDH* mutations. At this time, it is difficult to determine whether individuals with PGL and GIST but who are *SDH* mutation negative actually have Carney triad but have yet to develop the third component (Alrashdi et al. 2010). Because of the rarity of CSS and the short time from discovery of its genetic basis, one must assume that medical management and surveillance are similar to that recommended for those with PGL/pheochromocytoma syndromes caused by germline mutations in *SDHA-D* genes (see page 42).

### **Carney Complex (NAME Syndrome, LAMB Syndrome, Carney Syndrome) (OMIM 160980)**

Carney complex (CNC) is a rare autosomal dominant heritable multiple neoplasia syndrome characterized by cardiac, endocrine, cutaneous, and neural tumors and a variety of mucocutaneous pigmented lesions. CNC is linked to at least two different loci. Germline mutations in *PRKARIA*, on 17q22–q24, have been shown to cause a subset of CNC (Kirschner et al. 2000a, b). The gene on 2p15–p16, which may account for 20 % of all CNC families, has yet to be identified. Some believe that a third minor locus might also be involved.

This rare condition is characterized by cardiac, breast, and cutaneous myxomas, pigmented skin lesions, and micronodular pigmented adrenal hyperplasia (Koopman and Happle 1991). The tumors are commonly multicentric or bilateral, and the mean

age at diagnosis of the first manifestation is 18 years. Most patients have two or more manifestations of the condition. Pituitary adenomas and testicular tumors (Sertoli or Leydig cell in about 50 % of affected males) are associated, and the hormones secreted by these tumors cause characteristic phenotypic effects (Carney et al. 1986). Skin lesions include lentigines, blue nevi, dermal fibromas, and myxoid neurofibromas. The pigmentation is spotty, particularly on the face (in 70 % of cases), hands, and feet, and is similar to that seen in Peutz–Jeghers syndrome (PJS), although in the latter the lesions are seen more in the buccal region and palate, and the visceral lesions appear to be quite distinct in these two syndromes (Carney et al. 1985; Lodish and Stratakis 2011). Further, inner canthal pigmentation is virtually only seen in CNC. Eyelid myxomas are found in 16 % of affected patients. The tumors are usually benign, but liposarcomas and other malignant tumors may develop. The cardiac tumors are life threatening via embolism or by direct mass effect. Recently pancreatic cancer has been found in 9 of 354 cases of Carney complex (1 adenocarcinoma, 2 acinar cell carcinomas, and 3 intraductal mucinous neoplasms where histology was available), and loss of heterozygosity for *PRKARIA* was suggested, with lack of expression of the protein in 5/6 tumors studies (Gaujoux et al. 2011).

CNC was found to be linked to 17q22–q24 and 2p15–p16. Germline loss-of-function mutations in *PRKRIA*, encoding the type 1A subunit of the protein kinase A receptor on 17q22–q24, have been found in a subset of CNC (Kirschner et al. 2000a, b). Nonsense-mediated decay of mutant transcript appears to be the mechanism leading to loss of function (Kirschner et al. 2000a). Over 380 CNC patients with >20 years of follow-up in a bi-institutional series were analyzed for genotype–phenotype associations (Bertherat et al. 2009). There were 80 different germline *PRKRIA* mutations. Mutations in this gene were more commonly found in individuals with a combination of myxomas (affecting multiple organs), psammomatous melanotic schwannomas (PMS), thyroid tumors, and large cell calcifying Sertoli cell tumor (LCCSCT) than in individuals with CNC without this combination of clinical features. The “hot spot” mutation, c.491\_492delTG, was more commonly associated with lentigines, cardiac myxoma, and thyroid tumors than all other *PRKARIA* mutations combined (Bertherat et al. 2009). Individuals with isolated PPNAD tended to carry either the c.709-7 to c.709-2delATTTTT or c.1 A>G, and these are the only two mutations that have incomplete penetrance. In general, splice site mutations tended to occur with milder disease. Nonetheless, penetrance of *PRKARIA* mutation is >95 % by age 50 years. Germline *PDE11A* variation seems to modify germline *PRKARIA* mutations, conferring 4–5-fold increased prevalences of PPNAD and LCCSCT compared to those without *PDE11A* variants (Libe et al. 2011).

As with other inherited tumor syndromes, mutation analysis by bidirectional Sanger sequencing should begin with a clinically affected individual. Once a family-specific mutation in *PRKRIA* is found, then predictive testing may be offered. Clinical and biochemical screening for CNC and medical surveillance for affected patients remain the gold standard for the care of patients with CNC. In brief, for postpubertal pediatric and for adult patients of both sexes with established CNC, the

following annual studies are recommended: echocardiogram, measurement of urinary free cortisol levels (which may be supplemented by diurnal cortisol or the overnight 1 mg dexamethasone testing), and serum IGF1 levels (Stratakis et al. 1999). Male patients should also have testicular ultrasonography at the initial evaluation; microscopic LCCSCT (large cell calcifying Sertoli cell tumor) may be followed by annual ultrasound thereafter (Stratakis et al. 2001). Thyroid ultrasonography should be obtained at the initial evaluation, and may be repeated, as needed (Stratakis et al. 2001). Transabdominal ultrasonography in female patients is recommended during the first evaluation but need not be repeated, unless there is a detectable abnormality, because of the relatively low risk of ovarian malignancy (Stratakis et al. 2001). Because cardiac myxoma is responsible for a significant amount of morbidity and mortality, pediatric patients with CNC should have echocardiography during their first 6 months of life and annually thereafter; biannual echocardiographic evaluation may be necessary for patients with history of an excised myxoma.

### Cockayne Syndrome (OMIM 216400)

This is a very rare autosomal recessive disorder characterized by growth failure leading to extremely short stature, evident within the first few years after birth (described as “cachectic dwarfism”), lack of subcutaneous fat, cutaneous photosensitivity, deafness, progressive optic atrophy, neurological deterioration with a leukodystrophy, and mental retardation. There is brain dysmyelination with calcium deposits. There is a typical “salt and pepper” retinitis and/or cataracts. These features develop from late infancy, but there is considerable variability of the phenotype, even within families (Mahmoud et al. 2002). Characteristic facial features include large ears, sunken eyes, and limbs that are relatively long. There is type II hyperlipoproteinemia. Knee contractures may occur, causing a “horse-riding stance,” and delayed neural development and neurological degeneration cause mental retardation. Mean age at death is 12.5 years, but varies a great deal. There appears to be a deficiency of DNA repair after exposure to UV light and deficiency in cellular repair of oxidative DNA damage. Death usually occurs before the age of 20 years, and malignancy is not reported to be specifically increased in this condition. The disease is genetically heterogeneous, and genes for complementation groups CS-A and CS-B have been identified (Stefanini et al. 1996). Cockayne syndrome type A is caused by biallelic mutations in the gene encoding the group 8 excision repair cross-complementing protein (*ERCC8*; [www.omim.org/entry/609412](http://www.omim.org/entry/609412)) on chromosome 5q11. Cockayne syndrome type B (CSB; [www.omim.org/entry/133540](http://www.omim.org/entry/133540)) is caused by mutation in the *ERCC6* gene ([www.omim.org/entry/609413](http://www.omim.org/entry/609413)) on chromosome 10q11. Bertola et al. (2006) analyzed the *ERCC8* gene in Brazilian families with typical CSA and identified homozygosity or compound heterozygosity for *ERCC8* mutations in them, with no clear genotype/

phenotype correlation. The CS-B gene product is involved in transcription-coupled and/or global genome nucleotide excision repair of DNA damage induced by UV light and other oxidative DNA damage (Mahmoud et al. 2002; Osterod et al. 2002; Tuo et al. 2003). Notably, in contrast to human Cockayne syndrome, homozygous knockout mice for the murine orthologue of the human CSA gene (*Csa<sub>3/3</sub>*) develop skin tumors after chronic exposure to UV light (van der Horst et al. 2002). The reason why humans with Cockayne syndrome do not develop skin cancer is not known. Interestingly, other cases of Cockayne syndrome with features overlapping with those of xeroderma pigmentosum (XP) are due to mutations in the *XPB*, *XPD*, or *XPG* genes (Rapin et al. 2000). *XPG* and *CSB* mutations may also be responsible for the cerebro-oculo-facio-skeletal (COFS) syndrome (Graham et al. 2001). COFS is another autosomal recessive neurodegenerative disorder with growth failure, joint contractures, cataracts, microcornea, and optic atrophy.

## Celiac Disease

Patients with celiac disease have an increased risk of esophageal cancer, cancer of the mouth and pharynx, small bowel carcinoma, and lymphoma. Although non-Hodgkin lymphoma is the main cause of cancer death in celiac disease (Corrao et al. 2001), in a series of small bowel cancers, 13 % of adenocarcinoma cases and 39 % of lymphomas occurred in patients with celiac disease providing evidence that celiac disease confers susceptibility to adenocarcinoma of the small bowel as well as lymphoma (Howdle et al. 2003). Small bowel adenocarcinomas associated with celiac disease have a high frequency of microsatellite instability (MSI) and somatic inactivation of *MLH1* or *MSH2* (Potter et al. 2004). Although the absolute risk of malignancy in celiac disease is small, those cases complicated by malignancy often appear to have been poorly controlled, and treatment reduces the risk of malignancy (Houlston and Ford 1996; Ferguson and Kingstone 1996).

Celiac disease itself shows familial aggregation and a strong human leucocyte antigen (HLA) association. Familial clustering appears to reflect multifactorial inheritance with major genetic risk factors (HLA-DQ2 and HLA-DQ8) and environmental factors. It appears that genes within the HLA class II DQ region are necessary but not sufficient for celiac disease to develop. About 95 % of all patients have a DQ2 allele with DQ2 homozygotes being at highest risk. Of the remaining 5 %, most are DQ8 positive. It is estimated that HLA class II genes account for 50 % of genetic susceptibility to celiac disease, and non-HLA-associated genes are also implicated (Treem 2004). Hovhannisyan et al. (2008) showed that the HLA-DQ8 beta-57 polymorphism promotes the recruitment of T cell receptors bearing a negative signature charge in the complementary determining region 3-beta (CDR3-beta) during the response against native gluten peptides presented by HLA-DQ8 in celiac disease. These T cells showed a cross-reactive and stronger response to deamidated gluten peptides.

### **Common Variable Immunodeficiency (CVID) (OMIM 607594)**

This comprises a heterogeneous group of disorders characterized by hypogammaglobulinemia, humoral immunodeficiency, and susceptibility to infection. Some patients may also have defects in some aspects of cell-mediated immunity. Many cases are acquired, but genetic factors have been implicated in some cases, and autosomal recessive inheritance is proposed. There is an increased incidence of lymphoid malignancy in patients with common variable immunodeficiency (Kersey et al. 1988). In three families with a variant of CVID, a dominantly inherited combination of cold urticaria and antibody deficiency, with susceptibility to infection and autoimmunity, referred to as PLAID (PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation), researchers identified deletions in *PLCG2*. This led to gain in phospholipase C gamma 2 function and subsequent abnormal regulation of numerous leucocyte subsets (Ombrello et al. 2012). Cancers have not been reported in these families.

### **Constitutional Mismatch Repair Deficiency (CMMRD), also known as Autosomal Recessive Childhood Cancer Predisposition Syndrome (OMIM 276300)**

It has become appreciated that biallelic mutations in *MLH1*, *MSH2*, *MSH6*, and most commonly, *PMS2* can be responsible for an autosomal recessive condition characterized by mainly childhood and adolescent malignancies, particularly hematological (lymphomas and leukemias) and brain tumors, including medulloblastomas, glioblastomas, and oligodendrogliomata, other cancers (GI or uterine cancer), and dermatological features of NF (café-au-lait patches) (De Vos et al. 2004; Menko et al. 2004; reviewed in Wimmer and Etzler 2008). This has in the past been described as a variant of Turcot syndrome (p. 311) (De Rosa et al. 2000; Bougeard et al. 2003), and it is interesting to speculate what proportion of Turcot syndrome is attributable to mutations in APC and the MMR genes, particularly as both autosomal dominant and recessive forms of Turcot syndrome have been described.

### **Costello Syndrome (OMIM 218040)**

This rare multisystem condition is also known as fasciocutaneous syndrome and is usually sporadic, possibly representing new mutations. The facial features are similar to Noonan syndrome, with increasingly coarse features with age, and nasal papillomata. There is excess skin on the hands. Developmental delay after postnatal failure to thrive and short stature are usual. There is an increased risk of cancer, possibly up to 17 %, particularly rhabdomyosarcomas, neuroblastomas, and



transitional carcinomas of the bladder, and screening by 3–6-monthly abdominal ultrasound and 6–12-monthly urinary catecholamine estimations until 5 years of age and annual urinalysis thereafter recommended until 10 years of age (DeBaun 2002; Gripp et al. 2002, 2006).

The diagnosis is based on clinical findings, with confirmation of the diagnosis requiring identification of a germline heterozygous gain-of-function missense mutations in the *HRAS* proto-oncogene (Aoki et al. 2005; Gripp and Lin 2012). The mutation frequency is 90 %, with virtually all mutations involving exon 2 (first coding exon) of *HRAS*. Therefore, if the diagnosis is suspected but no *HRAS* mutation is found, then other differential diagnoses should be considered. Top differential diagnoses include other syndromes involving the RAS/MAPK pathway (so-called RASopathies) including type 1 neurofibromatosis (see p. 288), Noonan syndrome (see p. 297), cranio-cardio-facial syndrome, and Legius syndrome (Gripp and Lin 2012).

## Cowden Syndrome (Multiple Hamartoma Syndrome) (OMIM 158350)

Cowden syndrome (CS) is an autosomal dominantly inherited multiple hamartoma syndrome characterized by an increased risk of breast, thyroid, and endometrial cancer. Germline mutations in *PTEN*, encoding a lipid and protein phosphatase on 10q23.3, are associated with a subset (25–80 %) of CS (Eng et al. 2003; Zhou et al. 2003a, b; Eng and Peacocke 1998; Zbuk and Eng 2007; Tan et al. 2011).

Clinical diagnosis is often a challenge, because of the protean manifestations of CS, many of which can occur in isolation in the general population. For this reason, the true incidence is not known. After identification of *PTEN* as the CS gene, a molecular-based study revealed the incidence to be at least 1 in 200,000 (Nelen et al. 1997, 1999), although this is likely still to be an underestimate. Because CS is underdiagnosed, the proportion of apparently sporadic cases and familial cases (two or more affected individuals) is not precisely known. As a broad estimate, perhaps 40–65 % of CS cases are familial (Marsh et al. 1998; Marsh et al. 1999; Eng, unpublished observations, 2011).

The lack of uniform diagnostic criteria for CS prior to 1995 led to the formation of the International Cowden Consortium (C. Eng, Coordinator and Chair, [engc@ccf.org](mailto:engc@ccf.org)), which represented a group of centers mainly in North America and Europe interested in systematically studying this syndrome to localize the susceptibility gene. The consortium arrived at a set of consensus operational diagnostic criteria based on published data and expert opinion (Nelen et al. 1996; Eng and Parsons 1998). These criteria have been revised annually in the context of new molecular-based data and are reflected in the practice guidelines of the US-based National Comprehensive Cancer Network Genetics/High-Risk Panel (NCCN 1999; Eng 2000a, b; Hobert and Eng 2009) ([www.nccn.org](http://www.nccn.org) for 2005 and 2006 revisions which remain the best sets of criteria) as follows:

1. Pathognomic criteria:

- (a) Mucocutaneous lesions:
- Trichilemmomas, facial
  - Acral keratoses
  - Papillomatous papules
  - Mucosal lesions (e.g., scrotal tongue)
  - Lhermitte–Duclos disease (LDD)

2. Major criteria:

- (a) Breast carcinoma, invasive
- (b) Thyroid carcinoma, epithelial, especially follicular thyroid carcinoma and follicular variant of papillary thyroid carcinoma
- (c) Macrocephaly (megalencephaly) (>97th percentile)
- (d) Endometrial carcinoma

3. Minor criteria:

- (a) Other anatomic thyroid lesions, e.g., adenoma, multinodular goiter, Hashimoto's thyroiditis
- (b) Developmental delay
- (c) GI hamartomas (GI polyposis of any histology)
- (d) Fibrocystic disease of the breast
- (e) Lipomas
- (f) Fibromas
- (g) Genitourinary tumors (e.g., renal cell carcinoma, uterine fibroids) or malformation (e.g., bicornuate uterus, duplicated collecting ducts)

**Operational Diagnosis in an Individual:**

1. Mucocutaneous lesions alone if:

- (a) There are 6 or more facial papules, of which 3 or more are trichilemmomas
- (b) There are cutaneous facial papules and oral mucosal papillomatosis
- (c) There are oral mucosal papillomatosis and acral keratoses
- (d) There are palmoplantar keratoses, 6 or more

2. 2 Major criteria, but one must include macrocephaly or LDD

3. 1 Major and 3 minor criteria

4. 4 Minor criteria

**Operational Diagnosis in a Family Where One Individual Is Diagnostic for Cowden Syndrome (by Clinical Criteria or by Gene Status):**

1. Pathognomonic criterion/criteria

2. Any one major criterion with or without minor criteria

3. Two minor criteria

While the original intent of the International Cowden Consortium operational diagnostic criteria and the NCCN criteria were for the gene hunt (former) and for early clinical practice (both sets of criteria), the criteria would result in a dichotomous response, namely, meets criteria or does not meet criteria. Necessarily, these related two sets of operational criteria were based on retrospective data from exaggerated cases (full criteria mainly by pathognomic and major criteria) and familial cases. Recently, multiple logistic regression analysis of comprehensive *PTEN* mutation data from a >10-year prospective accrual of probands by a minimum of relaxed Consortium operational criteria from multiple centers, including the community, has resulted in a continuous score, the *PTEN* Cleveland Clinic Score ([www.lerner.ccf.org/gmi/ccscore/](http://www.lerner.ccf.org/gmi/ccscore/)), based on key phenotypic features (Tan et al. 2011). Because the key phenotypic features present in children and adults are quite different, two sets of criteria are utilized depending on age groups. A *PTEN* CC score of >10 in adults, relating to a prior probability of >3 % of finding a pathogenic *PTEN* mutation, was selected as the clinical threshold for considering *PTEN* testing/referral to genetic specialists (Tan et al. 2011).

More than 90 % of individuals affected with CS are believed to manifest a CS phenotype by the age of 20 years (Nelen et al. 1996; Eng 2000b). By the end of the third decade (i.e., 29 years), 99 % of affected individuals are believed to have developed at least the mucocutaneous signs of the syndrome, although any of a number of component features can manifest as well. The most commonly reported manifestations are mucocutaneous lesions; thyroid abnormalities; fibrocystic disease and carcinoma of the breast; multiple, early-onset uterine leiomyoma; and macrocephaly (specifically, megalencephaly) (Starink et al. 1986; Hanssen and Fryns 1995; Mallory 1995; Longy and Lacombe 1996; Eng 2000b; Ngeow et al. 2011).

The two most well-documented component malignancies are carcinomas of the breast and epithelial thyroid gland (Starink et al. 1986; Zbuk and Eng 2007; Hobert and Eng 2009). Historically, lifetime risks for female breast cancer are estimated to range from 25 to 50 % (Starink et al. 1986; Longy and Lacombe 1996) in contrast to 11 % in the general population. The age at diagnosis ranges between 14 and 65 years, with a mean around 40–45 years (Starink et al. 1986; Longy and Lacombe 1996). The histopathology of CS breast cancer is adenocarcinoma of the breast, both ductal and lobular (Schrager et al. 1997). Male breast cancer may be a minor component of the syndrome (Marsh et al. 1998; Fackenthal et al. 2001). In a recent prospectively accrued series of *PTEN* pathogenic mutation-positive CS and CSL cases, lifetime risk for female (invasive) breast cancer was calculated to be 85 % with age- and sex-adjusted standardized incidence rates (SIR) of >25 (Table 11.1) (Tan et al. 2012). This is much higher than pre-gene estimates and should be duly considered during risk management. Interestingly, this series did not note an elevated *PTEN*-related male breast cancer risk. The lifetime risk for differentiated thyroid cancer can be as high as 10 % in males and females with CS. A recent prospective series has revealed that individuals with germline pathogenic *PTEN* mutations have a 35 % lifetime risk of epithelial thyroid carcinoma (1) with SIR of 50–72 (Ngeow et al. 2011; Tan et al. 2012). In this large series, follicular thyroid

**Table 11.1** Lifetime risks of *PTEN*-related malignancies and age-related penetrance

Malignancy	Lifetime risk (%)	Penetrance by age 50 years (%)	Comments
Breast cancer	85	40	Females at risk only
Thyroid cancer		25	
Endometrial cancer	28	20	Females only
Colorectal cancer	10	1	
Renal cell cancer	34	10	
Melanoma	6	5	

carcinoma (FTC) was overrepresented among adults with *PTEN* mutations. While papillary thyroid carcinomas (PTC) were also observed, one-third of these were the follicular variant (FvPTC). All six children (<18 years of age) who were found to have pathogenic *PTEN* mutations had thyroid cancer, but interestingly all were PTC (Ngeow et al. 2011). With this new series, it is now obvious that the age at diagnosis of thyroid cancers is truly earlier (mean age 37.5 years) than that in the general population, and even children can develop PTC. Interestingly, *PTEN* frameshift mutations were found in 31 % of those with thyroid cancer and only 17 % of those who did not (Ngeow et al. 2011).

Endometrial carcinoma was also considered to be a putative component cancer of CS in previous genotype–phenotype and case studies (Marsh et al. 1998; DeVivo et al. 2000; Eng 2000b). In a prospective series of pathogenic *PTEN* mutation-positive CS and CSL cases accrued from academic and community-based healthcare facilities, the SIR of endometrial cancer was >40, with lifetime risk of 28.2 % (Table 11.1) (Tan et al. 2012). For the first time, elevated lifetime risks of renal carcinomas (34 %) and melanoma (6 %) were noted in *PTEN* mutation-positive individuals.

Prior to 2010, exponents believed that hamartomatous polyps were component of CS but that colorectal carcinomas were not part of the disease spectrum. However, in a recent prospective study of a series of individuals carrying pathogenic *PTEN* mutations, >90 % of those who received colonoscopies were found to have polyps (Heald et al. 2010). Surprisingly, polyps of all histologies and an elevated SIR (10–100) for colorectal cancers were noted, with the earliest age at diagnosis of cancer being 35 years and the oldest 50 years (Tan et al. 2012). The lifetime risk of *PTEN*-related colorectal cancer is almost 10 % (Tan et al. 2012). All but one person with colorectal cancer had pre-/coexisting colonic polyposis.

The most common nonmalignant component lesions include trichilemmomas (hamartoma of the infundibulum of the hair follicle) and papillomatous papules (90–100 %), thyroid adenomas and goiter (67 %), breast fibroadenomas and fibrocystic disease (75 %), macrocephaly (>80 %), and genitourinary abnormalities (40 %) including uterine fibroids and malformations (Mester et al. 2011; Ngeow et al. 2011). A rather striking nonmalignant hamartoma is LDD or dysplastic gangliocytoma of the cerebellum (Eng et al. 1994), which usually manifests later in life, initially with subtle degrees of dysmetria on intent, progressing to frank ataxia. A small series of incident LDD cases revealed that many adult-onset LDD carried germline *PTEN* mutations (Zhou et al. 2003a).

CS was mapped to 10q22–q23 (Nelen et al. 1996). Germline mutations in *PTEN* have been found in 85 % of CS probands diagnosed by the strict International Cowden Consortium criteria, when accrued by select academic centers (Marsh et al. 1998; Zhou et al. 2003b). In contrast, a large series accrued from the community revealed that ~25 % of probands meeting the strict International Cowden Consortium criteria were found to carry pathogenic *PTEN* mutations (Tan et al. 2011). These mutations result in loss of function, and the majority occur in exons 5, 7, and 8, which encode the phosphatase domain, although mutations can occur throughout the gene including the promoter (Zhou et al. 2003b). Germline mutations in *PTEN* have also been found in approximately 60 % of individuals with BRRS accrued from select academic tertiary referral centers (see section on Bannayan–Riley–Ruvalcaba syndrome, (BRRS) p. 221) (Marsh et al. 1997; 1999). Thus CS and BRRS are allelic. Compared to *PTEN* mutations in CS, mutations in BRRS tend to occur in the 3' half of the gene (Eng et al. 2003). There is a genotype–phenotype association in CS (Marsh et al. 1998): families found to have germline *PTEN* mutations have an increased risk of malignancy, in particular, breast cancer. The presence of both CS and BRRS features in a single family, of glycogenic acanthosis of the esophagus, or of LDD, increases the prior probability of finding a *PTEN* mutation (Marsh et al. 1999; McGarrity et al. 2003; Zhou et al. 2003b).

Germline *PTEN* mutations have also been described in up to 20 % of Proteus syndrome and up to 50 % of Proteus-like syndrome cases (Zhou et al. 2000, 2001; Smith et al. 2002). Germline mutations in *PTEN* have been described in single patients with megalencephaly and VATER association and with megalencephaly and autism (Dasouki et al. 2001; Reardon et al. 2001). Multiple studies of individuals with autism or autism with macrocephaly have now confirmed that *PTEN* mutations occur in ~10 % of those with autism spectrum disorder and macrocephaly (Butler et al. 2005; Herman et al. 2007; Varga et al. 2009).

It was puzzling that the *PTEN* mutation frequency in classic CS in the general population was 25 %, yet the original linkage studies suggested no genetic heterogeneity. Recently, a new gene named *KLLN* (encoding KILLIN) was discovered immediately upstream of *PTEN*, with *KLLN* and *PTEN* sharing a single bidirectional promoter. Germline epimutation (promoter methylation) of *KLLN* was shown to be associated with approximately one-third of CS and CS-like individuals who lacked germline *PTEN* mutations (Bennett et al. 2010). Interestingly, individuals with germline *KLLN* epimutation had a higher frequency of breast and renal cancers than those with germline pathogenic *PTEN* mutation (Bennett et al. 2010). The age-/sex-adjusted SIR for epithelial thyroid carcinoma for *KLLN* epimutation was found to be 45, but in contrast to *PTEN* mutation, classic PTC was overrepresented in those with *KLLN* epimutation (Ngeow et al. 2011). Finally, approximately 10 % of individuals with CS without germline *PTEN* mutations were shown to carry germline missense variants in *SDHB* or *SDHD* (Ni et al. 2008, 2012). Individuals carrying these *SDH* variants had a higher frequency of breast and thyroid cancers. Interestingly, individuals with germline *PTEN* mutations who also carry *SDHx* variants had a higher risk of breast cancer than those with germline *PTEN* mutations alone (Ni et al. 2012). Again, unlike CS with *PTEN* mutations, the thyroid cancers

found in cases with *SDH* mutations were mainly classic PTC (Ngeow et al. 2011). Recently, germline *AKT1* and *PIK3CA* mutations have been demonstrated in some cases of Cowden syndrome (Orloff et al. 2013).

All individuals with or suspected of having CS or any *PTEN*-related disorder should be referred to cancer genetic professionals. *PTEN* mutation analysis is a useful molecular diagnostic test and, in families with a known *PTEN* mutation, is a good predictive test. With the recent independent validation of germline *SDHx* variants in CS/CSL individuals (Ni et al. 2012), *SDHx* testing should also be seriously considered. Once the *KLLN* epimutation data are validated in independent series, *KLLN* should be considered in the armamentarium of CS testing.

Until now, surveillance recommendations are based on expert opinion, governed by the component neoplasia, breast carcinoma, epithelial thyroid carcinoma and adenocarcinoma of the endometrium, and now colonic polyps and cancer (Eng 2000b; Pilarski and Eng 2004; Heald et al. 2007; Hobert and Eng 2009) ([www.nccn.org](http://www.nccn.org)). Because of a recent prospective series of CS/CSL individuals, we suggest consideration of new potential surveillance recommendations based on the prospective risk data as outlined in Table 11.2 (Tan et al. 2012), although the cancer risk estimates are subject to ascertainment bias and may be overestimated in some series. For example, clinicians should consider thyroid examination and baseline ultrasound at diagnosis of CS or upon finding a mutation defining CS, even in children (Ngeow et al. 2011). Females should begin annual clinical breast examination and breast self-examination around the age of 25 years. Annual breast imaging (mammography, breast MRI) should begin at 30 years. Because of accumulating data on *PTEN*-related colonic polyposis and cancer, colonoscopic surveillance could begin by 35–40 years or 5 years younger than the youngest age at diagnosis of colon cancer in the family (Heald et al. 2010; Levi et al. 2011) (Table 11.2). The optimal interval for colonoscopies is currently unknown, but could be modified by polyp load. In the past, the recommendation was for the endometrium to be screened clinically beginning at the age of 35–40 years or 5 years younger than the earliest age of endometrial cancer diagnosis in the family: annual blind repeat biopsies prior to menopause and transabdominal ultrasound after menopause. The NCCN in its recent (2009 onwards) revisions has removed endometrial screening because no formal evaluation studies have been completed. However, in view of the new prospective data which have yielded a much higher lifetime risk of endometrial cancer than previously believed, endometrial surveillance could be reconsidered (Table 11.2) (Tan et al. 2012). Clinicians who look after CS patients should be mindful to note any other seemingly non-component neoplasias, which might be overrepresented in a particular family as well.

With the elucidation of the *PTEN*-AKT-mTOR signaling pathway, targeted therapeutics hold great promise. mTOR inhibitors are being used in clinical trials for Cowden syndrome patients, specifically *PTEN* hamartoma tumor syndrome, and efficacy has been demonstrated in a related phakomatosis, tuberous sclerosis complex, and in the somatic setting in malignancies where upregulation of mTOR signaling is evident.

**Table 11.2** Recommendations for diagnostic workup and cancer surveillance in patients with *PTEN* mutations

	Pediatric (<18 years)	Adult male	Adult female
Baseline workup	Targeted history and physical examination  Baseline thyroid ultrasound Dermatological examination Formal neurological and psychological testing	Targeted history and physical examination  Baseline thyroid ultrasound Dermatological examination	Targeted history and physical examination  Baseline thyroid ultrasound Dermatological examination
Cancer surveillance			
From diagnosis	Annual thyroid ultrasound and skin examination	Annual thyroid ultrasound and skin examination	Annual thyroid ultrasound and skin examination
From age 30 <sup>a</sup>	As per adult recommendations		Annual mammogram (for consideration of breast MRI instead of mammography if dense breasts)  Annual endometrial sampling or transvaginal ultrasound (or from 5 years before age of earliest endometrial cancer in family)
From age 40 <sup>a</sup>	As per adult recommendations	Biannual colonoscopy <sup>b</sup> Biannual renal ultrasound/MRI	Biennial colonoscopy <sup>b</sup>  Biennial renal ultrasound/MRI
Prophylactic surgery	Nil	Nil	Individual discussion of prophylactic mastectomy or hysterectomy

<sup>a</sup>Surveillance may begin 5 years before the earliest onset of a specific cancer in the family, but not later than the recommended age cutoff

<sup>b</sup>The presence of multiple nonmalignant polyps in patients with *PTEN* mutations may complicate noninvasive methods of colon evaluation. More frequent colonoscopy should be considered for patients with a heavy polyp burden

## Denys–Drash Syndrome (OMIM 194080)

This rare disorder is characterized by male pseudohermaphroditism, Wilms tumor, and a characteristic glomerulonephropathy causing progressive renal failure. Not all patients have the complete triad, and nephropathy plus Wilms tumor or urogenital abnormalities are sufficient to make the diagnosis. Wilms tumor in Denys–Drash syndrome presents early (mean age 18 months) and is usually bilateral (Jadresic et al. 1991). Gonadoblastoma may also occur. The nephropathy is characterized by



focal or diffuse glomerulosclerosis and typically presents with proteinuria, progressing to nephrotic syndrome and hypertension, and then reaching end-stage renal failure by 3 years of age (Coppes et al. 1993). Males (XY karyotype) with Denys–Drash syndrome usually have ambiguous genitalia or phenotypically normal female external genitalia (male pseudohermaphroditism). In addition, the internal genitalia are frequently dysplastic or inappropriate (Mueller 1994).

The risk of Wilms tumor in children with truncating *WT1* mutations or missense mutations in the zinc finger domains (as is typical for Denys–Drash syndrome) is estimated to be >50 %, and screening with 3–4 monthly renal ultrasonography is recommended (Scott et al. 2006). Indeed the risk of Wilms tumor in Denys–Drash syndrome is high enough for bilateral prophylactic nephrectomy to be suggested for children with incomplete Denys–Drash syndrome (e.g., pseudohermaphroditism, hypogonadism, and renal failure) (Hu et al. 2004). Molecular genetic analysis of patients with this syndrome has demonstrated de novo germline *WT1* mutations in most cases (Royer-Pokora et al. 2004). The majority of mutations affect the zinc finger domains and are thought to have a dominant negative effect on genital development (Little et al. 1993). Denys–Drash syndrome is allelic with Frasier syndrome.

## Down Syndrome (OMIM 190685)

The risk of acute leukemia in Down syndrome (DS) (trisomy 21) is 20–30 times that of the general population. This increased risk relates both to acute lymphoblastic and acute myeloid leukemia (AML). The cumulative risk of leukemia in DS is 2.1 % by age of 5 years and 2.7 % by age of 30 years. The most common type is acute nonlymphocytic leukemia subtype M7-megakaryocytic leukemia, a type very rare in individuals with normal karyotypes. Acute megakaryoblastic leukemia (AMKL) is particularly prevalent, with an estimated 500-fold increased risk compared to the general population, and a transient form of AMKL, transient myeloproliferative disorder (TMD), is seen in about 10 % of newborn cases with DS, which usually resolves, but about 20 % will develop AMKL within the first 4 years of life (Hasle et al. 2000; Klusmann et al. 2007; Rabin and Whitlock 2009). Leukemia comprises about 60 % of all malignancies and 90 % of all childhood malignancies in DS. The standard incidence rate (SIR) for leukemia in DS is 56 at 4 years and 10 at 5–29 years of age. This risk is particularly pronounced for AML, usually early onset, 49 % developing below 1 year of age (Hasle 2001). AML-M after myelodysplastic syndrome is characteristic, as is trisomy 8 with reduced granulocyte lineage. Leukemic clones in DS are nearly always megaloblastic with *GATA1* (zinc finger transcription factor required for erythroid and megakaryocytic development) mutations conferring a clonal advantage (Groet et al. 2003). Leukemic blasts in DS-AMKL harbor mutations in *GATA1*, which encodes a hematopoietic transcription factor. Most mutations cluster in exon 2 resulting in a truncated mutant protein, GATA1s, lacking the amino-terminal transcriptional activating domain. These

mutations are also demonstrable at birth, thus representing an early intrauterine event, and a persistent subclone of TL cells may develop into AMKL as a result of additional mutations (Hitzler and Zipursky 2004).

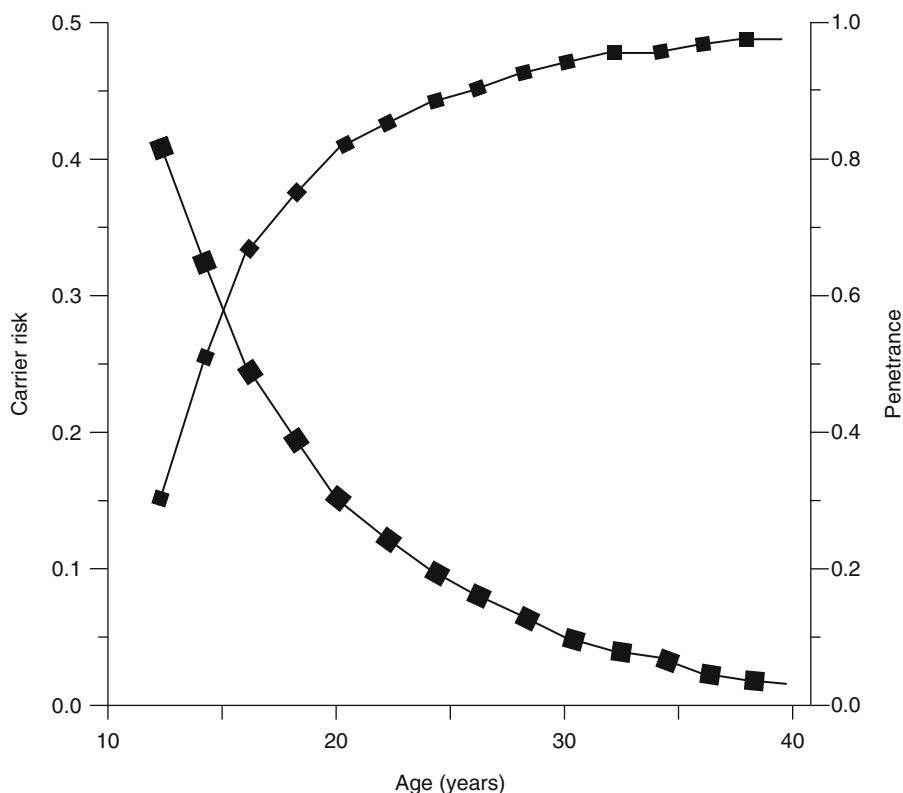
There is an increased frequency of *JAK2R683* mutations in acute lymphoblastic leukemia in Down syndrome. The overall occurrence of solid tumors (especially breast cancer) in DS is reduced, except for retinoblastoma and germ cell tumors (Look 2003).

## Familial Adenomatous Polyposis (OMIM175100)

This is the most common of the hereditary polyposis syndromes, with a prevalence of about 1 in 8,000. It is inherited as an autosomal dominant trait with high penetrance but variable age at onset, and the mutation rate is high (15–20 % of cases are considered to be new mutations, although this may be an overestimate, and some single generation cases may be due to biallelic germline mutations in *MUTYH*) (Sieber et al. 2003a, b). Some sporadic cases (about 15 %) are mosaic for the *APC* mutation. Polyps usually develop in the teens, and penetrance is almost complete by age of 40 years in classical cases (Fig. 11.1). Progression to malignancy is inevitable, and colorectal carcinoma develops in untreated cases by the fourth to fifth decade, or even in childhood, 20–30 years earlier than in nonfamilial colon cancer. Histologically, single crypt adenomas are a characteristic feature. Polyps also occur elsewhere in the GI tract. Gastric polyps in FAP are of two types: benign hyperplastic fundic gland polyps occur in most patients, and adenomas may also occur, usually in the pyloric region of the stomach, but at a much lower frequency. Gastric cancer may develop, even in young patients. Adenomatous duodenal polyps occur in most patients with FAP (over 80 %), are most numerous around the ampulla of Vater, and are associated with a significant risk of malignant transformation. The severity of duodenal polyposis is assessed using the Spigelman scale. Duodenal cancer is now the leading cause of death in this condition if colorectal cancer is prevented and occurs in about 5 % of cases (Spigelman et al. 1995; Brosens et al. 2005; Groves et al. 2002). Carcinoma of the gallbladder and bile ducts may also occur.

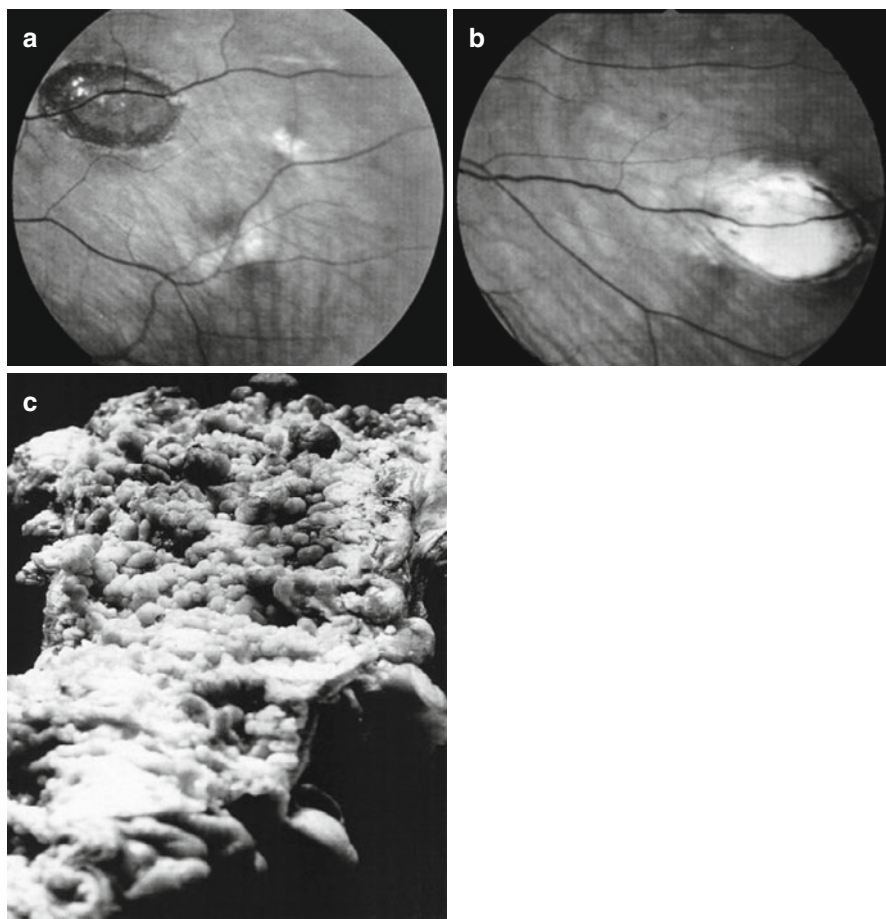
Extra-intestinal lesions develop in most patients with FAP and may be apparent before the bowel lesions. Epidermoid cysts may occur in two-thirds of patients, and although they can develop anywhere on the body, they are most noticeable on the scalp. These are very rare in normal children before puberty. Osteomas of the mandible may be detected in more than 90 % of patients using orthopantomograms and are uncommon in the general population (4 %). A third of patients may have impacted teeth, and dentigerous cysts and supernumerary and unerupted teeth may occur. Exostoses may develop in the skull, digits, and long bones, and cortical thickening is described.

The most common extraintestinal manifestation of FAP is multiple areas of retinal pigmentation, called congenital hypertrophy of the retinal pigment



**Fig. 11.1** Age-related carrier risk (*larger squares*) for relatives at 50 % prior risk of FAP, that is an affected parent, and a negative bowel examination at that age. The age-related risk was derived from the age-related penetrance data (*smaller squares*) (Adapted from Burn et al. 1991, with permission from J. Burn)

epithelium (CHRPE). These are found in about three-quarters of affected individuals. These are discrete, darkly pigmented, rounded lesions, 50–200 mm in diameter, and may have depigmentation around them (Fig. 11.2). Smaller, solitary, unilateral lesions may be seen in normal people, but it is rare for normal individuals to have more than three lesions. In FAP four or more CHRPEs are often present, characteristically large, oval, pigmented lesions with surrounding halo (type A lesions) which are specific for FAP; CHRPEs in controls are usually small dots (type B) (Olschwang et al. 1993). The larger lesions are probably congenital and appear to be choristomas of myelinated axons; the small lesions may show enlarged retinal pigment epithelial cells with increased pigment (Parker et al. 1990). There are interfamilial differences in predisposition to CHRPE in FAP, related to the position of the mutation in the *APC* gene, mutations distal to exon 9 being more prone to be associated with such lesions (Bunyan et al. 1995). However, there are exceptions to this (Pack et al. 1996), and there is intrafamilial variability in numbers of CHRPEs (Hodgson et al. 1994). Nevertheless, it has



**Fig. 11.2** FAP: (a) pigmented CHRPE, (b) depigmented CHRPE, and (c) florid colonic polyposis (Reproduced with permission from Cambridge University Press)

been estimated that in families in which CHRPEs appear to be a feature of the disease, the finding of fewer than three lesions in an individual at 50 % risk reduces the carrier risk, whereas the presence of more than three lesions conveys a very high probability that the individual is affected (Burn et al. [1991](#)).

### Frequency of Complications in FAP:

- Congenital hypertrophy of the retinal pigment epithelium (70–80 %)
- Thyroid cancer (2–3 %)
- Epidermoid cysts (50 %)
- Brain tumor (1 %)
- Osteoma (50–90 %)
- Hepatoblastoma (1 %)

- Desmoid tumor (10–15 %)
- Supernumerary teeth (11–27 %)
- Adrenal gland adenomas (7–13 %)

(Adapted from Vasen et al. 2009)

Desmoid disease is common in FAP, occurring in about 10–15 % of cases. It is nearly twice as common in females as in males and occurs at an earlier age in females (Brosens et al. 2005). Desmoids are more common in some families than in others, and this is related to the position of the germline APC mutation (mutations beyond codon 1444 being more likely to cause the disease). Histologically, they are composed of very vascular, fibrous tissue and may be diffuse or encapsulated. They occur predominantly in the small bowel mesentery, peritoneum, or abdominal wall, although they occasionally develop at extra-abdominal sites and often develop after a surgical procedure or pregnancy; 10 % resolve; 50 % may remain stable for prolonged periods; 30 % fluctuate; and 10 % grow rapidly. Desmoid tumors do not metastasize but do infiltrate locally and can cause major morbidity and death, being one of the most common causes of death in FAP. They tend to recur after surgery, so treatment with nonsteroidal anti-inflammatory drugs (sulindac), antiestrogens, or, in resistant cases, cytotoxic chemotherapy or radiotherapy with computerized tomography monitoring is preferable.

Extraintestinal cancers associated with FAP include papillary carcinoma of the thyroid, brain tumors (medulloblastoma, astrocytoma), and hepatoblastoma. Papillary carcinoma of the thyroid, characteristically the cribriform variant, appears to occur at increased frequency in young women (under 35 years of age) with FAP and in individuals with specific mutations in the APC gene, particularly at codon 1061 (Fenton et al. 2001). Brain tumors (especially astrocytomas) are rare overall, but the relative risk is high in individuals with FAP: 23 to age of 29 years for all brain tumors (7 for all ages) and 99 to age of 29 years for cerebellar medulloblastomas. Some cases of Turcot syndrome are a variant of FAP (see p. 311). A number of cases of hepatoblastoma have been described in children with FAP, and although the absolute risk is small, the relative risk is high (<500), and screening might be considered in high-risk families, although not usually performed (Hirschman et al. 2005).

Classically, the diagnosis of FAP is made clinically by the finding of more than 100 adenomatous polyps in the colon and rectum, with histological evidence of single crypt adenomas. However, there is a milder form of the disease, attenuated FAP (AFAP), characterized by the presence of fewer adenomas and later onset of disease, which is seen in about 8 % of cases. The differential diagnosis is from other causes of intestinal polyposis, most importantly MUTYH-associated polyposis (p. 287) and other causes of inherited bowel cancer, such as Lynch syndrome and individuals with germline mutations in *POLD1* and *POLE* (Palles et al. 2013). Individuals with AFAP usually have fewer than 100 adenomas, and such a phenotype may be caused by mutations in the first 4 exons of the APC gene (Olschwang et al. 1993; Knudsen et al. 2010) or by biallelic mutations in *MUTYH*. Biallelic germline *MUTYH* mutations have been assessed as causing 30 % of cases of >15 and <100 and 8 % classical polyposis with no APC mutation (Sieber et al. 2003a, b).

The FAP gene (*APC*) was localized to chromosome 5q21 following the report of a mentally retarded man who had Gardner syndrome and a constitutional deletion of chromosome 5q (Herera et al. 1986). Characterization of the mutation in the *APC*

gene in an affected individual in the family (possible in >90 % cases) allows predictive testing to be made available to at-risk relatives. The gene is large and has 15 exons, of which exon 15 is the largest. Most mutations in FAP patients are frame-shift (2/3) or nonsense (1/3) mutations which result in the production of a truncated protein (Nagase and Nakamura 1993). Many different mutations have been described, but there are common ones, at codons 1061, 1450, and 1309 in exon 15. The *APC* gene product functions as a tumor suppressor with subcellular location and interaction with catenins. It contains a number of coiled-coil heptad repeats at the 5' end that promote oligomerization; the central part of the gene contains beta-catenin-binding domains, involved in cell-cell interaction, and Armadillo repeats, and the 3' end contains tubulin-binding domains, with properties of binding to microtubules (Ilyas and Tomlinson 1997; Fodde et al. 2001).

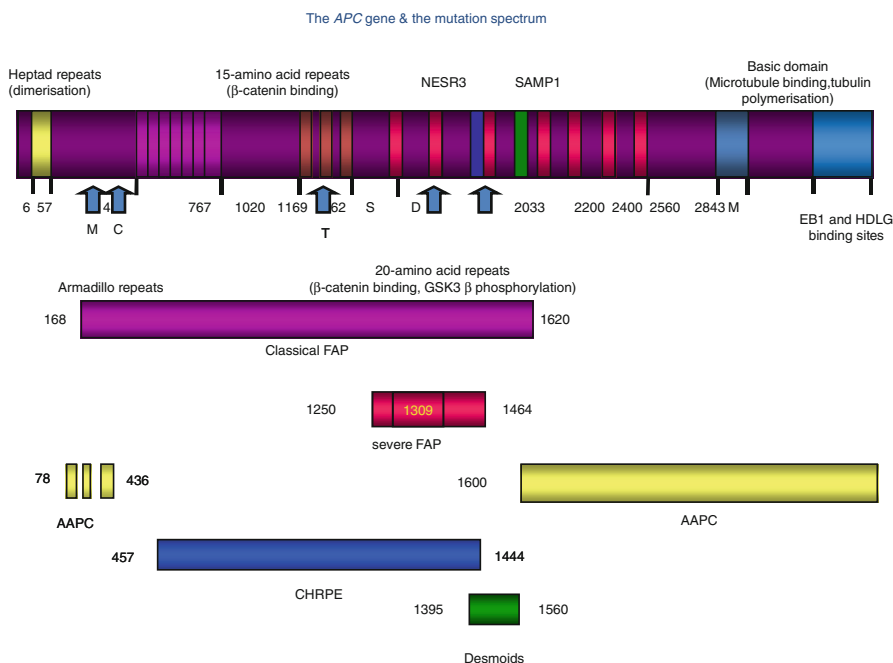
Phenotype-genotype correlations are apparent (Stormorken et al. 2007), with the common mutations (1309 and 1061) being associated with a severe phenotype (Nugent et al. 1994), mutations before exon 9 usually being associated with a lack of CHRPE, and mutations in the first 6 exons being associated with a more variable and often milder phenotype, including "attenuated FAP" (Foulkes 1995). *APC* mutations found in "attenuated FAP" most commonly occur in exon 4, but many individuals with this "attenuated" form do not appear to have *APC* mutations; some may have *MUTYH*-associated polyposis. The observation that very short variant proteins may result in a less severe phenotype tends to support the "dominant negative" theory, but large deletions of the gene may be found in individuals with a severe phenotype, so that other factors including the loss of the mild *APC* mutant allele (Spirio et al. 1998) or the effects of other polymorphic alleles such as at the *NAT1* and *NAT2* genes (Crabtree et al. 2004) may also be involved in the pathogenesis of the disease process.

Usually there is reasonable consistency with regard to severity of adenomatous disease in different individuals with FAP within a single family, but some exceptions to this have been reported, with very variable age at onset of polyps in different cases, some presenting decades later than their affected relatives (Evans et al. 1993).

The frequency of extracolonic features in FAP is associated with mutations in specific regions of the *APC* gene (Fig. 11.3).

The phenotypic effects of a germline *APC* mutation may be affected by FAP modifier genes which include *MOM* in mice and genes encoding DNA methyltransferase and COX-2 (Fearon 1997; Crabtree et al. 2002, 2003).

A polymorphism in the *APC* gene was detected in an individual with a family history of colorectal cancer but not polyposis. Subsequent analysis suggested that this germline T-A mutation, predicted to result in a change from isoleucine to lysine position 1307 of the protein, predisposed to the development of somatic mutations of the *APC* gene and that gene carriers were therefore predisposed to colorectal cancer without florid polyposis, with a twofold increase in risk of bowel cancer in mutation carriers (Rozen et al. 2002). The mechanism for this at a molecular level appears to be that the polymorphism which converts an AAATAAAA sequence to (A)8 predisposes to the development of somatic mutations in the *APC* gene. This mutation is almost entirely restricted to the Ashkenazim (about 6 % of the Ashkenazi population probably carry this variant) (Laken et al. 1997), and there has been much debate about whether population screening for this mutation should be advocated in Ashkenazim, with colonoscopic



**Fig. 11.3** The APC gene and the mutation spectrum The frequency of extracolonic features in FAP is associated with mutations in specific regions of the APC gene (With permission from Ian Tomlinson) AAPC attenuated FAP, T thyroid cancer

surveillance for gene carriers. Currently the increase in risk is not thought to be sufficient for such a measure to be appropriate. Other germline variants such as E1317Q may be associated with an attenuated phenotype (Lamlum et al. 2000), but the evidence for this is less clear (Hahnloser et al. 2003), and recent data suggest that there is no increased colorectal neoplasia risk in carriers of this variant (Theodoratou et al. 2008).

## Management

Surveillance of the colorectum in patients at risk of FAP should begin before the age of 20 years; the risk of developing colorectal cancer before this age is very low, but some affected individuals do develop severe polyposis before the age of 10 years, so endoscopic surveillance should be commenced between 11 and 15 years, earlier if symptoms related to colonic problems occur beforehand (Vasen et al. 2008). Flexible sigmoidoscopy is probably sufficient before the age of 20 years as the polyps almost invariably develop in the distal colon initially, but colonoscopy should be performed annually from 20 years until florid polyposis develops.

Patients with FAP should be offered total colectomy with ileorectal anastomosis or proctocolectomy with restorative ileoanal anastomosis once colonic polyps have developed (Church 2006). The risk of colorectal cancer is significant once polyps



have begun to develop, irrespective of polyp density (Phillips and Spigelman 1996). After surgery conserving the rectal stump, subsequent management should include lifelong surveillance of the rectal stump by yearly sigmoidoscopy as there is a 3.5 % risk of colorectal cancer in it after 5 years, rising to 10 % at 10 years. Proctocolectomy removes this risk and may be done after 50 years of age. In addition, since upper GI cancer is reported to occur in 5 % of patients, with an estimated prevalence of duodenal dysplasia of up to 90 %, initial surveillance by means of upper GI endoscopy with a side-viewing endoscope to allow detailed examination of the papilla, or a forward-viewing endoscope in early Spigelman stage cases, recommended to start at about 25 years of age, to give a baseline for subsequent follow-up (Arvanitis et al. 1990; Debinski et al. 1995; Theodoratu et al. 2008) (Fig. 11.4). If adenomas are detected, they should be biopsied; larger adenomas may be removed and further surveillance continued with 1–5-yearly duodenoscopy, depending on the Spigelman severity score (Dunlop 2002; Vasen et al. 2008). Duodenal cancer in FAP patients below 30 years of age is extremely rare, and the overall risk of duodenal cancer is small (5 %), but with a Spigelman stage III–IV, the risk of cancer is 7–36 %.

Palpation of the thyroid gland and possibly ultrasound in young women with FAP have been suggested, but the rarity of death from thyroid cancer in this disease makes this of questionable benefit unless there is a family history of thyroid cancer, and this is not usually performed.

Relatives of affected individuals should be ascertained with the help of a genetic register, and those at risk of inheriting the disease should be offered screening and genetic testing if possible. Screening of at-risk relatives is commenced between the ages of 11 and 13 years by annual sigmoidoscopy because the rectum is involved by adenomas at an early stage, and polyps rarely develop before 11 years of age. However, if symptoms arise, it may be necessary to arrange endoscopy earlier because there are case reports of colonic polyps developing in young children (Distante et al. 1996). Where the APC mutation has been characterized, predictive testing may be offered to children in the family, and once a child has been found to carry the APC mutation in the family, it is appropriate to consider colonoscopy in their early teens to establish the extent of polyposis. In an at-risk child where a predictive genetic test is not available, if polyps are found, these are biopsied (to confirm they are adenomatous and to exclude malignancy) and colonoscopy is arranged. Although small numbers of polyps can be managed by endoscopic resection, because of the inevitability of florid polyposis developing and the risk of malignant change, definitive surgery (see above) is usually arranged at this stage. In the absence of positive findings, sigmoidoscopy is continued annually, with colonoscopies with dye spray after 20 years of age, to exclude more proximal polyposis. This is continued to at least the age of 40 years, by which time the risk to an individual with an affected parent has fallen below 1 % (see Fig. 11.1). However, since very variable age at onset has been described in some families, it is advisable to continue screening well beyond this age (Evans et al. 1993). Endoscopic surveillance should also be offered to individuals with attenuated polyposis and their close relatives (Heiskanen et al. 2000), with colonoscopic surveillance 2-yearly from age 18–20 years, and upper GI surveillance as for classical FAP (Debinski et al. 1995; Vasen et al. 2008). If colectomy is necessary, ileorectal anastomosis should be offered; since the risk of duodenal cancer is also present, upper GI surveillance should also be recommended as above.

Spigelman Score of Duodenal Polyposis			
criterion	1 point	2 points	3 points
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology Dysplasia	Tubular Mild	Tubulovill. Moderate	Villous Severe

**Fig. 11.4** Spigelman score of duodenal polyposis

Predictive testing based on mutation analysis may be available, and individuals who have not inherited the mutation can be discharged from follow-up. A more cautious approach to management is indicated where the predictive test was based upon linkage analysis, surveillance being indicated until the estimated chance that the individual is affected is calculated as below 0.1 % on Bayesian risk analysis combining clinical and molecular data. Prenatal diagnosis is available by mutation or linkage analysis in informative families, although the uptake rate is low. The acceptability of such testing in a disorder such as FAP is a very personal matter, and the decision about whether to opt for such testing should be one made by the family after nondirective genetic counseling. Many parents wish their children to be tested for FAP at a very young age, but there are arguments for delaying such testing until clinical screening would normally be instituted, since, until this time, clinical management would not be affected (Hyer and Fell 2001).

The effectiveness of intervention strategies, such as the administration of aspirin, are being evaluated (Mathers et al. 2003), but are not sufficient to obviate the need for colectomy in affected individuals once polyps have developed. In FAP, the CAPP1 study showed that aspirin had a modest effect on polyp progression and significantly reduced the size of the largest polyps in 200 FAP patients, but no effect on polyp number (Burn et al. 2011). There has been some evidence that the administration of oral sulindac (a nonsteroidal anti-inflammatory drug) or cyclooxygenase-2 (COX-2) inhibitors in general may cause regression of duodenal

adenomas (Phillips et al. 2002). Carcinoma of the rectal stump may occur (in about 10 % of cases) after surgical removal of the colon and ileorectal anastomosis, and COX-2 inhibitors may also be effective in reducing polyp recurrence in the colorectum (Steinbach et al. 2000), but these have been shown to increase cardiovascular morbidity in the VICTOR and APPROVE research studies and are therefore not recommended – but there is a delayed effect on colorectal cancer incidence, as seen in the CAPP2 study. Fish oils have long been thought to be protective against GI cancers, and a special formulation of eicosapentaenoic acid (EPA) was able to reduce polyp number and size (West et al. 2010).

## Fanconi Anemia (OMIM 227650)

Fanconi anemia (FA) is an autosomal recessive chromosomal instability disorder which is characterized by congenital abnormalities, defective hemopoiesis and a high risk of developing AML and certain solid tumors. The birth incidence of FA is around 3 per million. Affected individuals can have mild growth retardation (63 %), and median height of FA individuals lies around the 5th centile. Other clinical features include areas of skin hyper- and hypopigmentation (64 %), skeletal defects (75 %) including radial limb defects (absent thumb with or without radial aplasia), abnormalities of ribs and hips, scoliosis, and cardiac (13 %) and renal (34 %) malformations. Other associated anomalies include microphthalmia (38 %) and developmental delay (16 %). The phenotypic abnormalities are variable and there is marked variability between affected individuals in the same sibship. Importantly, up to one-third of FA cases do not have any obvious congenital abnormalities and are only diagnosed when another sibling is affected or when they develop a hematological problem. However, most FA cases do have some subtle clinical features, such as dermatological manifestations.

The pancytopenia usually develops between the ages of 5 and 9 years (median age 7 years), and symptoms due to this develop progressively. The cumulative incidence of any hematological abnormality in FA is up to 90 %, and the cumulative incidence of leukemia is around 10 % by age of 25 years. The crude risk (irrespective of age) for MDS is around 5 % and for leukemia is 5–10 % (Alter et al. 2003). FA patients that survive into early adulthood are around 50 times more likely to develop solid tumors compared to the general population, and in one study 29 % developed a solid tumor by the age of 48 years (Rosenberg et al. 2003). In particular, there is a high risk of hepatic tumors (which may be related to androgen use) but also squamous cell carcinomas of the esophagus, oropharynx, and vulva (Alter 2003; Rosenberg et al. 2003).

The hallmark feature of FA cells is chromosomal hypersensitivity to DNA cross-linking agents such as mitomycin C (MMC) or diepoxybutane (DEB), and the resulting increase in chromosome breakage provides the basis for a diagnostic test (Auerbach 1993). The characteristic chromosomal findings are excess tri- and quadriradial and complex interchanges. The basic defect appears to be a deficiency of the repair of DNA strand cross-links. The relationship between the DNA repair

defects and chromosomal aberrations found in this condition and the susceptibility to cancer is not fully understood; an increased mutation rate or incidence of tumor-promoting translocations may be a factor.

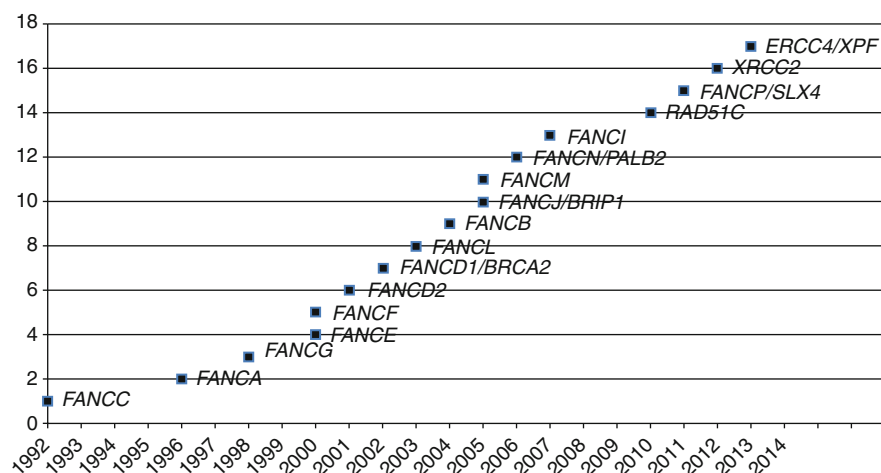
There is some evidence that heterozygotes for FA have an increased risk of certain cancers, especially leukemia and gastric and colonic cancers, with a relative risk of 3 reported, but this did not reach statistical significance (Swift et al. 1980; reviewed in Tischkowitz and Hodgson 2003). A separate study of 125 relatives of FA patients failed to reproduce these observations (Potter et al. 1983), and a more recent study of 36 UK families also found no excess of cancers in relatives of FA cases (OR 0.97,  $P=0.62$ ) (Tischkowitz et al. 2008). Chromosome breakage testing in FA heterozygotes is complicated by overlap with the normal range (Pearson et al. 2001). Prenatal diagnosis has been achieved by demonstrating increased spontaneous and induced chromosome breakage in fetal cells (cultured amniocytes or chorionic villus cells) (Auerbach et al. 1985).

Sixteen FA genes have been identified since 1992 (see Fig. 11.5). *FANCA* mutations account for almost two-thirds of cases, *FANCC* and *G* for 25 %, and *FANCE* and *FANCF* for a further 8 %. There are only a handful of FA cases that have not yet been genetically diagnosed. Diagnosis by direct mutation detection is available. Molecular studies have established that a common pathway exists, both between the FA proteins and other proteins involved in DNA damage repair, such as *NBS1*, *ATM*, *BRCA1*, and *BRCA2* (reviewed in Venkitaraman 2004).

*FANCD1* has been shown to be *BRCA2* (Howlett et al. 2002). FA cases due to biallelic *BRCA2* mutations are rare but seem to be associated with an increased risk of medulloblastoma or Wilms tumor that may precede development of aplastic anemia (Hirsch et al. 2004; Offit et al. 2003) or an earlier onset of leukemia (Wagner et al. 2004). A family history of breast or ovarian cancer might provide clues in these cases. At present it is not known whether such cases should have intensive screening for solid tumors or whether they would benefit from more aggressive treatment with earlier stem cell transplants. The finding that FA can be caused by biallelic *BRCA2* mutations should be taken into account when counseling *BRCA2* mutation carriers, although interestingly no homozygosity for some frequent mutations, such as 6174delT, has been identified.

Perhaps not surprisingly, *PALB2* (partner and localizer of *BRCA2*) has also been found to be a FA gene (*FANCN*, arrow on figure), and like *BRCA2/FANCD1*, children with biallelic *PALB2/FANCN* mutations tend to have more serious cancer-related phenotypes, with early-onset Wilms Tumor, acute myeloid leukemia, and medulloblastomas predominant (Reid et al. 2007; Xia et al. 2007; Tischkowitz and Xia 2010). The *BRCA1* partner, *BRIP1* (also known as *BACH1*), is also a FA gene – *FANCF* (Levrin et al. 2005; Levitus et al. 2005). Notably, children with FA type J tend to develop solid tumors, rather than the leukemia seen with *FANCD1/BRCA2* and *FANCN/PALB2*.

Continuing the DNA damage repair/cancer/FA theme, a handful of children with FA or FA-like disorders have been found to carry biallelic mutations in *XRCC2* (Shamseldin et al. 2012) or *RAD51C* (Vaz et al. 2010). In contrast to the genes mentioned above, cancer has yet been noted in these children. Interestingly, while



**Fig. 11.5** Tempo of discovery of 16 FA genes (Figure courtesy of Marc Tischkowitz MD, PhD)

some data have suggested that monoallelic *XRCC2* mutations seem to moderately increase the risk for breast cancer (Park et al. 2012), monoallelic *RAD51C* mutations predispose to ovarian cancer only (Meindl et al. 2010; Loveday et al. 2011).

Until recently it was thought that biallelic *BRCA1* mutations were embryonic lethal, but such a case has now been described in an individual who had short stature, microcephaly, developmental delay and was diagnosed with ovarian carcinoma at age 28 (Domchek et al. 2013). She was found to have one allele with a *BRCA1* c.2457delC (p.Asp821Ilefs\*25) truncating mutation, and a hypomorphic c.5207T>C missense mutation (p.Val1736Ala) on the other allele. This possibly unique combination of clinical features resemble FA, but are likely distinct from it. Unfortunately DEB testing was not carried out and cannot be done as the patient has died.

At diagnosis patients should have a full hematological assessment that should include examination of the bone marrow; HLA typing in anticipation of possible bone marrow transplantation should be performed. Other investigations at presentation should include audiometry, ultrasound of the renal tract, an endocrine assessment, especially if there is evidence of growth failure, and an ophthalmology assessment. Referral to hand surgeons and plastic surgeons may be indicated to consider correction of radial ray defects with a view to improving function and appearance. It is important that siblings are also tested as they may not have any congenital abnormalities.

If there is no hemopoietic defect at time of diagnosis, hematological monitoring may only be required once per year, but as the patient becomes older and develops hematological complications, hematologists play an increasingly central role. Many patients who develop bone marrow failure initially respond to treatment with androgens and hemopoietic growth factors. Eventually most patients become refractory to these therapies, and the definitive treatment currently available for bone marrow failure is hemopoietic stem cell transplantation.

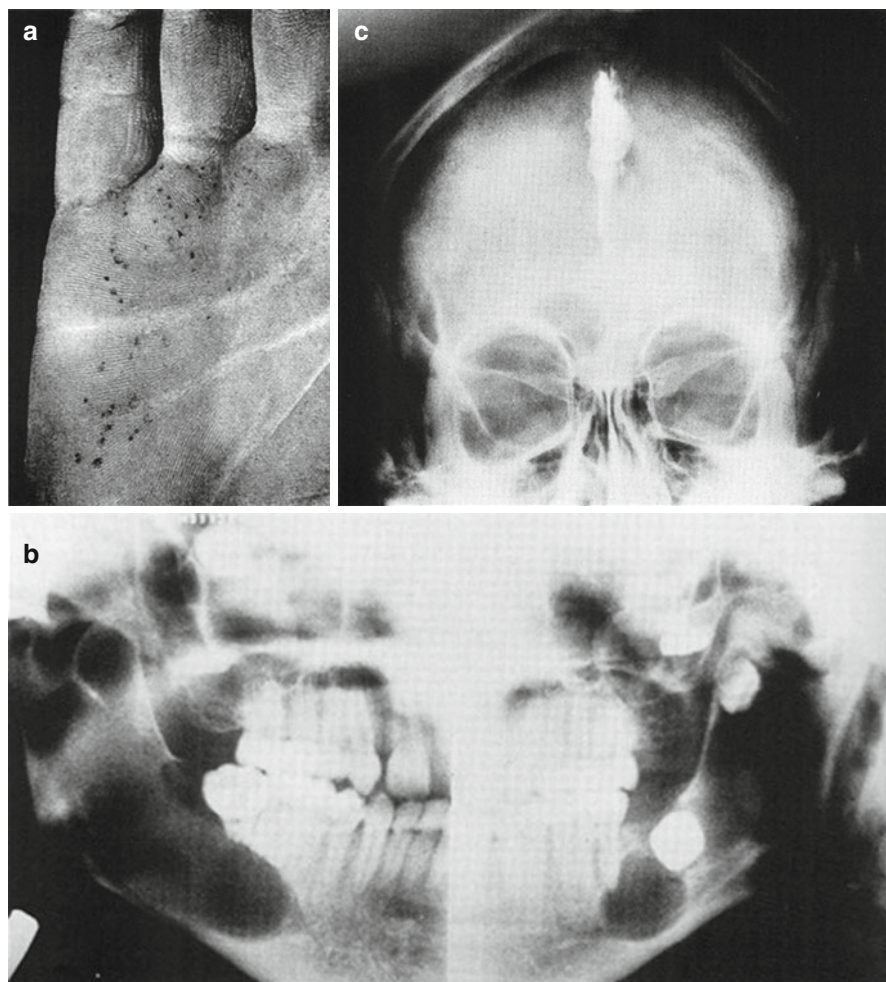
## **Frasier Syndrome (OMIM 136680)**

This disorder is caused by mutations in the *WT1* gene and so is allelic with Denys–Drash syndrome. It is characterized by male pseudohermaphroditism, streak gonads, and steroid-resistant nephritic syndrome and renal failure from focal and segmental glomerulosclerosis, but although gonadoblastoma is frequent, the risk of Wilms tumor is much less, and the glomerulopathy progresses more slowly than in Denys–Drash syndrome. The risk of Wilms tumor has been estimated at 5–10 % risk, and affected children should also be offered surveillance by 3–4-monthly renal ultrasonography (Scott et al. 2006). The *WT1* intron 9 splicing mutations that cause Frasier syndrome alter the balance of WT1 isoforms (Klamt et al. 1998) and cause Frasier syndrome if the karyotype is 46,XY and isolated nephrotic syndrome if the karyotype is 46,XX (Chernin et al. 2010).

## **Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome) (OMIM 109400)**

This is an autosomal dominant condition with a minimal prevalence of 1 in 70,000 of the population. The main features of this syndrome are multiple basal cell carcinomas (BCC) of the skin (most common in sun-exposed areas) and palmar and plantar pits (occurring in 65 % of cases) (see Fig. 11.6a). The basal cell skin lesions arise as pink or brown papules from the age of puberty onwards. Only 15 % manifest before puberty, and 10 % or more of patients have no skin lesions at the age of 30 years. They mainly affect the thorax, neck, and face. UV light increases the incidence of the BCC; they are more common in white-skinned patients, and therapeutic radiation is often associated with progression of BCC that is present within the radiation field. Only a small proportion of carcinomas become locally invasive, but they can cause severe destruction, particularly around the eyes and orifices. Metastasis is very rare. There are many associated non-dermatological features, including hypertelorism with a broad nasal bridge and frontal and parietal bossing and a prominent chin. Odontogenic keratocysts of the jaw are common (see Fig. 11.6b). These are multiple, usually bilateral, recurrent, and slow growing and occur in 85 % of mutation carriers by the age of 40 years. Squamous cell carcinomas have been reported within keratocysts in patients with Gorlin syndrome who have been treated by radiotherapy for facial BCC (Moos and Rennie 1987). Variable skeletal abnormalities are associated, including “bridging” of the sella with calcification of the falx cerebri (see Fig. 11.6c); bifid (usually third, fourth, or fifth), absent, or rudimentary ribs fusion defects of the cervical spine; polydactyly or syndactyly, short fourth metacarpals, flame-shaped lucencies of the metacarpals and/or phalanges, and Sprengel deformity. Ocular abnormalities have been reported, including exotropia, chalazia and coloboma, and congenital blindness. All except the skeletal features increase with age, but there is considerable variability of expression of these features in different affected people





**Fig. 11.6** Gorlin syndrome: (a) palmar pits, (b) odontogenic keratocysts and (c) calcified falx cerebri (courtesy of Robert Gorlin). Reproduced with permission from Cambridge University Press

(Gorlin 1987, 1995). The condition is inherited as an autosomal dominant trait with almost complete penetrance but highly variable expression. Diagnostic features are described in Table 11.3.

A variety of other, less common, abnormalities have been noted in affected people, including milia, epidermoid cysts, chalazia and comedones of the skin, cleft lip and palate, pectus carinatum, and hypogonadotropic hypogonadism in males. Hamartomatous upper GI polyposis has also been reported (Schwartz 1978). There is a definite increase in incidence of non-dermatological malignancies, including squamous cell carcinoma and fibrosarcoma in the jaw cysts, and nasopharyngeal carcinomas. Mental retardation has been reported in about 3 % of cases, but its true



**Table 11.3** Diagnostic criteria for Gorlin syndrome (Evans et al. 1993)*Major criteria*

More than two BCCs or one BCC under 20 years at diagnosis

Histologically proven odontogenic keratocysts of the jaw

Three or more cutaneous palmar or plantar pits

Bifid, fused, or markedly splayed ribs

First-degree relative with Gorlin syndrome

*Minor criteria*

Height-adjusted macrocephaly

*One of the following orofacial characteristics:* cleft lip or palate, frontal bossing, coarse face, moderate or severe hypertelorism

*One of the following skeletal abnormalities:* Sprengel, pectus excavatum (marked), severe syndactyly

*One of the following radiological features:* bridging of the sella turcica, hemi-/fused/elongated vertebral bodies, modeling defects and flame-shaped lucencies of the hands and feet

Ovarian fibroma, medulloblastoma

The diagnosis requires the presence of two major or one major and one minor features

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incidence is unclear. Detailed CT and MRI have revealed a high incidence of asymmetric or dilated ventricles in 24 %, and one in ten individuals has dysgenesis or agenesis of the corpus callosum (Kimonis et al. 2004). Childhood medulloblastoma may occur in the first 2 years of life, and meningioma and craniopharyngioma have been described. Bilateral ovarian fibromas (which can be hormonally active) are common in affected women, and there is a risk of ovarian fibrosarcoma or other malignancy developing in these lesions (Ismail and Walker 1990).

Seminoma has been reported in males. Cardiac fibromas may occur from early childhood; these may remain static or possibly regress or enlarge with age. Other tumors that have been described in association with Gorlin syndrome include renal fibroma, melanoma, neurofibroma, leiomyoma, and rhabdomyoma/sarcoma. Mesenteric lymphatic or chylous cysts may occur.

Surveillance of affected people should consist of yearly dermatological examinations and 6-monthly evaluation of the jaw cysts by means of an oropantogram, since odontogenic cysts can erode locally and be very destructive, and early enucleation of these cysts can prevent this. Infants should be kept under surveillance for signs of medulloblastoma, and some have recommended 6-monthly MRI until the age of 7 years (after which the risk declines significantly) (Kimonis et al. 2004). Cranial ultrasound may also be a useful investigation because care should be taken to restrict exposure to radiation to a minimum in view of the extreme radiation sensitivity in this condition. Pelvic ultrasound scanning may detect ovarian tumors, but in view of the low incidence of this complication, regular scanning is generally not advised.

Genetic counseling should be facilitated by molecular genetic analysis. Affected children may show few features. However, if at the age of 5 years an at-risk child has no abnormality on X-ray of spine or skull and has no osteomas or dermatological lesions, the risk of the child being a gene carrier is very small (Farndon et al. 1992).

Gorlin syndrome is caused by mutations in the human homologue (*PTCH*) of the *Drosophila* segment polarity gene *patched* which maps to chromosome 9q (Hahn et al. 1996; Johnson et al. 1996). There is no evidence of locus heterogeneity in Gorlin syndrome, and most reported mutations are predicted to cause protein truncation. No genotype–phenotype relationships have been identified (Wicking et al. 1997). *PTCH* encodes a transmembrane glycoprotein that acts as an antagonist in the Hedgehog signaling pathway. *PTCH* inhibits smoothened (SMO), which in turn activates transcription factors in the *Wnt* and decapentaplegic pathways. It appears likely that some manifestations of Gorlin syndrome (e.g., symmetrical developmental defects, such as macrocephaly) result from haploinsufficiency but that basal cell carcinomas and other tumors require inactivation of both alleles in a two-step mechanism of tumorigenesis (Levanat et al. 1996). Interestingly, too much activity in the Hedgehog pathway leads to Gorlin syndrome with the associated cancer risk, whereas underactivity causes holoprosencephaly (Roessler et al. 1997; Odent et al. 1999).

## Hemihypertrophy/Hemihyperplasia

Isolated hemihypertrophy/hemihyperplasia (IH) refers to asymmetric regional body overgrowth secondary to abnormal cell proliferation in individuals without any other underlying diagnosis. IH should be distinguished from hemiatrophy and from asymmetrical overgrowth that can be associated with Beckwith–Wiedemann syndrome (BWS), proteus syndrome, neurofibromatosis type 1, mosaic trisomy 8, and disorders associated with vascular malformations such as Klippel–Trenaunay syndrome. IH may be associated with a significant risk of learning disability, genitourinary abnormalities, and neoplasia (Viljeon et al. 1984). The most frequently associated neoplasm is Wilms tumor, but there are also reported associations with adrenal cortical tumors and hepatoblastoma (Viljeon et al. 1984). Estimates of the tumor risks associated with IH are variable (e.g., risk of Wilms tumor 1 to 3 % (Viljeon et al. 1984; Dempsey-Robertson et al. 2012)) and may be influenced by ascertainment bias. In a prospective study of 168 children for 10 years, the tumor incidence was ~6 % (6 Wilms and 2 adrenal cortical carcinomas out of the total of 10 tumors) (Hoyme et al. 1998).

There is overlap between the molecular abnormalities described in BWS (e.g., paternal uniparental disomy for chromosome 11p15.5, imprinting center 1 epimutations) and those detectable in a subset of patients with IH (Grundy et al. 1991). However, it has been suggested that the results of such testing cannot reliably distinguish between those children who will and will not develop an embryonal tumor and that tumor surveillance (abdominal ultrasound every 3 months until 7 years and serum alpha-fetoprotein measurement every 3 months until 4 years) should be offered to all children with IH (Clericuzio and Martin 2009). In contrast, Scott et al. (2006) recommended that abdominal ultrasound screening should only be offered to children with hemihypertrophy with paternal uniparental disomy 11p15 or isolated *H19* hypermethylation.

## Hereditary Non-polyposis Colorectal Cancer, Lynch Syndrome (OMIM 120435)

*This condition is commonly abbreviated as HNPCC and now preferably termed Lynch syndrome.*

### ***Background: History and Epidemiology***

Lynch et al. (1985) delineated two disorders characterized by an autosomal dominantly inherited predisposition to colon cancer without florid polyposis. These disorders, “Lynch syndromes I and II” (the latter reserved for families with extracolonic cancers), are not distinct entities (Lynch et al. 1993). Paradoxically, in some “HNPCC” pedigrees, colorectal cancer is absent and led to the reintroduction of the term “Lynch syndrome” to describe this condition (Umar et al. 2004a). The condition is due to inherited changes in the DNA mismatch repair (MMR) genes, most commonly *MLH1*, *MSH2*, and *MSH6* and less frequently *PMS2*. Early studies suggested that in most affected individuals, there is a high risk of colon cancer, up to 80 % lifetime risk, somewhat lower in females (40 %) than in males (Dunlop et al. 1997), with an early age at diagnosis of colon cancer (40–50 years compared with 60–70 years in the general population), a preponderance of right-sided tumors (60–70 % versus 15 %), and susceptibility to multiple primary cancers (25 % versus 5 %) and metachronous cancers (23 %) (Lynch and de la Chapelle 1999), and about 5 % of colorectal cancers occur before 30 years of age (Vasen et al. 2001).

In individuals with Lynch syndrome, there is a predisposition to a variety of extracolonic cancers, most commonly endometrial but also ovarian, gastric, pancreatic, hepatobiliary tract, urothelial, and small intestine (Watson and Lynch 2001). Estimates of the cumulative lifetime risks of the various cancer types in gene mutation carriers are 28–78 % for colorectal cancer in males (24–52 % in females), 27–72 % for endometrial cancer in women, 19 % for gastric cancer, 18 % for biliary tract cancer, 1–12 % for urinary tract cancer and 3–13 % for ovarian cancer in women, and with a 1–4 % risk of brain tumors and 4–7 % risk of small bowel tumors, representing a significantly increased relative risk for these tumor types (reviewed in Vasen et al. 2007). The estimated cumulative risks of colorectal cancer by age 70 years in individuals with Lynch syndrome have been reported as 41 % (95 % confidence intervals [CI], 25–70 %) for *MLH1* mutation carriers, 48 % (95 % CI, 30–77 %) for *MSH2*, and 12 % (95 % CI, 8–22 %) for *MSH6*. For endometrial cancer, corresponding risks were 54 % (95 % CI, 20–80 %), 21 % (95 % CI, 8–77 %), and 16 % (95 % CI, 8–32 %). For ovarian cancer, they were 20 % (95 % CI, 1–65 %), 24 % (95 % CI, 3–52 %), and 1 % (95 % CI, 0–3 %). The estimated cumulative risks by age 40 years did not exceed 2 % (95 % CI, 0–7 %) for endometrial cancer or 1 % (95 % CI, 0–3 %) for ovarian cancer. The estimated lifetime risks for other tumor types did not exceed 3 % with any of

the gene mutations (Bonadona et al. 2011; Aarnio et al. 1995, 1999; Barrow et al. 2013). These risks are lower than those published previously.

The estimated relative risks for extracolonic cancer vary with different germline mutations: those for small intestinal cancer are 291 for *MLH1* mutation carriers and 102 for *MSH2* mutation carriers; for gastric cancer 4 and 19, respectively; for ovarian cancer 6 and 8, respectively; and for urinary tract cancer 75 in *MSH2* mutation carriers only (Vasen et al. 2001). Overall, *MSH2* mutations appear to confer a higher risk of cancer than *MLH1* mutations, mainly due to an increased risk of urinary tract and endometrial cancers in *MSH2* mutation carriers. *MSH6* mutations are associated with less of a risk of colorectal cancer but an increased risk of endometrial and, to a lesser extent, urothelial cancer (Wijnen et al. 1999; Vasen et al. 2001).

### ***Clinical Features and Pathology***

Florid polyposis does not occur in Lynch syndrome, but colonic adenomas (particularly right sided) have been reported to be more common than in controls: 30 % of Lynch syndrome patients have at least one colonic adenoma, and 20 % have multiple lesions, compared with 11 and 4 % in age- and sex-matched controls (Lanspa et al. 1990; Gaglia et al. 1995). Other studies have, however, suggested that the prevalence of adenomas is not greatly increased, but they develop more rapidly through the adenoma–carcinoma sequence in this disease (Jass 1995). If multiple adenomas do occur, it is very rare to find more than 50, which differentiates Lynch syndrome from FAP, in which characteristically there are more than 100 polyps. A subgroup of patients with Lynch syndrome develop flat adenomas (slightly elevated lesions with adenomatous changes confined to the colonic crypts) (Lynch et al. 1990a, b, c), although it is not clear that this subset can be distinguished by molecular means.

The MMR defect results in instability of microsatellite DNA in the tumors, causing microsatellite instability (MSI) in over 90 % tumors in Lynch syndrome compared with 15 % in sporadic tumors.

The pathology of colorectal cancers in Lynch syndrome is notable for a slight overrepresentation of mucinous carcinomas, mainly well differentiated and rarely of the signet-ring cell type, with a medullary pattern in about 9 % of cases. Lymphocytic infiltration and tumor budding with de-differentiation are more common in Lynch syndrome than in sporadic cancers, and in Lynch syndrome, there are characteristically more *APC*, *CTNNB1*, and *KRAS* mutations than in sporadic cancers, whereas DNA methylation and *BRAF* mutations are rare (Jass 2004). Interestingly, a higher level of antibody reactivity against such frameshift peptides (FSPs) can be demonstrated in patients with microsatellite unstable Lynch syndrome and healthy MMR mutation carriers than in controls, indicating that these FSPs are recognized by the patients' T cells. This may account for the observed high levels of inflammatory response with lymphocyte infiltration in tumors in individuals with Lynch syndrome.

The dermatological features of Muir–Torre syndrome (Smyrk et al. 2001) with sebaceous adenomas and carcinomas may occur occasionally in individuals with Lynch syndrome, but genotype–phenotype correlations are not evident, beyond the observation that *MSH2* mutations are more likely to cause this than *MLH1* (Lucci-Cordisco et al. 2003).

Turcot syndrome is defined as the co-occurrence of colorectal polyps and brain tumors (see p. 311). This can be caused by germline mutations in the *APC* gene or germline mutations in one of the MMR genes. Some children have been described with adenomatous colonic polyps, primary brain tumors, leukemia, and café-au-lait skin patches, with an autosomal recessive inheritance pattern, and the condition has been shown to be due to homozygosity or compound heterozygosity for mutations in the MMR genes *MLH1*, *MSH2*, *MSH6* or *PMS2* (Ricciardone et al. 1999; Whiteside et al. 2002; Menko et al. 2004, reviewed in Bandipalliam 2005) (see p. 232).

There is evidence that colorectal cancers exhibiting MSI have a better survival than those that do not (Bubb et al. 1996; Gryfe et al. 2000), and this may also be true for those with Lynch syndrome (Sankila et al. 1996; Watson et al. 1998), although this has been disputed (Farrington et al. 2002; Clark et al. 2004).

Diagnostic Features

For practical purposes, and for research, criteria for the diagnosis of Lynch syndrome known as the Amsterdam criteria were drawn up in 1991 (see Table 11.4).

Table 11.4 The original Amsterdam criteria: AC1

1. At least three relatives (all related to each other) affected by colorectal cancer, one a first-degree relative of the other two
2. At least two successive generations affected
3. Colorectal cancer diagnosed before 50 years of age in one relative
4. Familial adenomatous polyposis excluded

Vasen et al. (1991); Reproduced with permission from Dr. H. Vasen

Table 11.5 The revised Amsterdam criteria: AC2

1. At least three relatives (all related to each other) affected by a Lynch syndrome-related cancer, <sup>a</sup> one a first-degree relative of the other two
2. At least two successive generations affected
3. Lynch syndrome-related cancer diagnosed before 50 years of age in one relative
4. Familial adenomatous polyposis excluded

Vasen et al. (1999); Reproduced with permission from Dr. H. Vasen

<sup>a</sup>The only cancers permitted are colorectal carcinoma, endometrial adenocarcinoma, small intestinal adenocarcinoma, transitional cell carcinoma of the renal pelvis, and transitional cell carcinoma of the ureter

**Table 11.6** The revised Bethesda guidelines

Tumors from individuals should be tested for MSI in the following situations	
1.	Colorectal cancer diagnosed in a patient who is less than 50 years of age
2.	Presence of synchronous, metachronous colorectal, or other Lynch syndrome-associated, tumors, regardless of age
3.	Colorectal cancer with the MSI-H histology (such as tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient who is less than 60 years of age
4.	Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome-related tumor, with one of the cancers being diagnosed under age 50 years
5.	Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome-related tumors, regardless of age

Adapted from Umar et al. (2004a, b)

Subsequently, because of the increased relative risk for the related tumors referred to above, the occurrence of an endometrial or upper GI carcinoma in a young individual in such a family was included to indicate affected status with regard to Lynch syndrome (Amsterdam 2 (AC2) criteria; Vasen et al. 1999; Aarnio et al. 1995, 1999) (see Table 11.5).

The seven-point Bethesda guidelines were introduced to increase the sensitivity of diagnosis, identifying 94 % of patients with a pathogenic mutation, but with low specificity (25 %) (Rodriguez-Bigas et al. 1997). These guidelines were introduced initially to indicate who might benefit from MSI analysis, not to replace the Amsterdam criteria, which was originally designed to identify families most likely to carry mutations in the causative genes. On the basis of further research into the sensitivity and specificity of the original guidelines, they have recently been changed, simplified, and in some ways made broader (Umar et al. 2004a). These guidelines differ from the original in that fulfilling the Amsterdam criteria is no longer included, the presence of colonic adenomas alone is not sufficient for inclusion, and the age at diagnosis for inclusion has been (Table 11.6).

A logistic model that takes into account various clinical parameters of the family has been proposed to estimate the probability of a mutation being present in *MLH1* or *MSH2* (Wijnen et al. 1998). One study showed that in a high-risk clinical setting, virtually all *MLH1* and *MSH2* mutation carriers can be identified by applying only the first 3 of the original 7 Bethesda guidelines; on the other hand, the specificity is substantially reduced (Syngal et al. 2000). However, *MSH6* mutation carriers tend to be diagnosed with cancer at a later age than individuals with inherited mutations in *MLH1* and *MSH2* (median 66 years at diagnosis) and are more often rectal in site (Klarsov et al. 2011); they are less likely to be diagnosed using the above criteria. Studies in the population have indicated that identifying all mutation carriers using family history alone is not possible (Aaltonen et al. 1998). Other models (such as the so-called “Amsterdam-Plus” model) have tried to improve on previous models by including additional information such as the number of family members with one or more adenoma or double primary cancers (Lipton et al. 2004). Further improvements incorporating molecular markers found in the cancers may soon be

possible, and there is an argument for looking for microsatellite instability (MSI) or immunohistochemical staining for the MMR proteins in all colorectal cancers in individuals affected below a certain cutoff age, such as 60 years. A series of recommendations have been established for the process of evaluation of at-risk patients; see below (Wijnen et al. 1997; Vasen et al. 1989, 1995).

Recommendations for the process of molecular evaluation of patients identified as being at risk, based on meeting the Bethesda guidelines (adapted from Umar et al. 2004a) modified recently, suggest doing immunohistochemical staining (IHC) first, using four antibodies in patients with family histories conforming to criteria for Lynch syndrome, but doing MSI analysis first in families with a less strong family history (Vasen et al. 2007). This is because MSI is very sensitive (almost 100 %), but although less sensitive, immunohistochemistry (IHC) can indicate the gene to test for germline mutations. False positives with IHC may occur and are probably due to the antibody detecting a truncated form of the protein. MSH6 staining is usually absent in cases due to a *MSH2* mutation (although the reverse is not observed) and is not always abnormal in tumors arising in *MSH6* mutation carriers (Berends et al. 2002). Tumors in individuals with Lynch syndrome characteristically demonstrate MSI, but this may also occur in 15 % of all colorectal cancers. Testing the tumor for MSI using a panel of microsatellites (BAT 25, BAT 26, and three others) helps to identify tumors from individuals with an increased likelihood of having Lynch syndrome (Boland et al. 1998), but as more microsatellites are used, the number of MSI-high tumors increases, and the test becomes less specific for Lynch Syndrome (Laiho et al. 2002; Reyes et al. 2002). The yield of mutations (positive predictive value) in families meeting the Amsterdam criteria is about 50 % and sensitivity 40 %, while the yield in families meeting the Bethesda criteria is 10–20 % and the sensitivity is about 90 %.

*MLH1* methylation is common (86 %) in MSI-high tumors from non-Lynch syndrome subjects (de la Chapelle 2004), so lack of such methylation makes Lynch syndrome more likely. *BRAF* mutations are rarely seen in Lynch syndrome-related cancers, and their presence in a colorectal cancer occurring in a hereditary colorectal cancer family makes a MMR gene mutation unlikely (Wang et al. 2003a, b). Taken together, these observations suggest that pathological analysis of colorectal cancers can considerably simplify germline mutation analysis in hereditary colorectal cancer families:

1. The optimal approach to evaluation is MSI or immunohistochemical analysis of tumors, followed by germline MMR gene testing in patients with MSI-H tumors or tumors with a loss of expression of one of the MMR genes.
2. After the mutation is identified, at-risk relatives can be referred for genetic counseling and predictive testing.
3. An alternative approach, if tissue testing is not feasible, is to proceed directly to germline analysis of the MMR genes, but this is not currently cost-effective, but may become more attractive if MMR gene mutations are offered as part of cancer panel gene testing.
4. If no MMR gene mutation is found in a proband with an MSI-H tumor and/ or a clinical history of Lynch syndrome, the genetic test result is non-informative.



The patients and the at-risk individuals should be counseled as for Lynch syndrome, and high-risk surveillance should be undertaken.

## ***Molecular Genetics***

The most common genes in which germline mutations may cause this disease are *MSH2* on chromosome 2p16, *MLH1* on chromosome 3p21 which account for approximately 90 % of cases of Lynch syndrome, *MSH6* on 2p15, and much less commonly, *PMS2* on chromosome 7p22, which can be a rare cause of childhood brain cancer, when biallelic mutations are present (De Vos et al. 2004, see pages 9, 226 and 304 for more details). Mutations in *MSH3* are very rarely reported in patients with colorectal cancer (Nicoliaides et al. 1994; Akiyama et al. 1997; de la Chapelle 2004). Interpretation of reported mutations in *PMS2* is complicated by the presence of pseudogenes (Hayward et al. 2004). Up to one-half of individuals diagnosed with colorectal cancer before the age of 35 years may have a germline mutation in one of these genes (Liu et al. 1995), but only a minority of patients with colorectal cancer diagnosed between the ages of 35 and 45 years without a family history of colorectal cancer have such mutations. The overall contribution of Lynch syndrome to colorectal cancer is probably 2–3 % (de la Chapelle 2004), but only extensive, multimodal mutation analysis can find more than 75 % of all mutations. Alu-mediated exonic deletions are particularly common in *MSH2*.

All these genes are involved in the same pathway for repair of mismatches in DNA, and MSI may be demonstrated as DNA replication errors detectable in tumor relative to genomic DNA (Parsons et al. 1993; Liu et al. 1995; Shia et al. 2005). Frameshift mutations of the transforming growth factor (TGF) type II receptor gene (*TGFBR2*) and other growth-/apoptosis-related genes such as *BAX* are common and are due to the runs of mono- or dinucleotide repeats present in these target genes. Analysis of a series of families with Lynch syndrome suggests that perhaps half of the cases are due to mutations in the *MSH2* gene, 30–40 % to mutations in the *MLH1* gene, less than 10 % are attributable to mutations in *MSH6*, and only a handful are due to mutations in other genes. When multiple analysis techniques are used, most families that fulfill the Amsterdam Criteria are found to have germline Lynch syndrome mutations (DiFiore et al. 2004; Wagner et al. 2003). Founder mutations in the genes causing Lynch syndrome are known; for instance, there is an *MLH1* deletion of exon 16 in the Finns (Nystrom-Lahti et al. 1995), and a founder mutation in *MSH2*, known as p.Ala636Pro, probably accounts for a third of all Lynch syndrome cases in the Ashkenazi Jewish population (Foulkes et al. 2002). Attenuated forms of FAP may rarely masquerade as Lynch syndrome, usually due to unusual mutations in the *APC* gene (Spirio et al. 1993). Other genes that may be involved in colorectal cancer predisposition, with single reports of germline mutations reported in cases, include *AXIN2* and *TGFBR2*. Subsequent data have suggested that the latter mutation is most likely to be a neutral polymorphism (Lu et al. 1998; de la Chapelle 2004).

A small minority of cases of Lynch syndrome can be caused by constitutional *MLH1* epimutations, with soma-wide allele-specific promoter methylation and transcription silencing of this gene. These epimutations are reversible, resulting in non-Mendelian inheritance of the phenotype. These were initially identified in cases with early-onset colorectal cancer showing loss of staining for *MLH1* and MSI in the tumor, but with no identified germline mutation in the *MLH1* gene. Deletion of the unmethylated *MLH1* gene was demonstrated in the tumor (Hitchins and Ward 2009). In many cases the somatic methylation was mosaic, and the case sporadic, but some familial cases have been described, with apparent variability in the degree of somatic methylation of the *MLH1* gene. The risk of a Lynch syndrome phenotype in the first-degree relatives of such cases is less than 50 %, as the methylation defect appears to be unstable, leading to non-Mendelian inheritance patterns, but it is recommended that first-degree relatives of cases should be screened as for Lynch syndrome.

Constitutional epimutations in *MSH2* have been detected in some cases of Lynch syndrome with loss of staining for *MSH2* and *MSH6*, and MSI, in tumor samples, but with no detectable germline mutation in *MSH2*. In these cases a germline deletion mutation has been detected in the final exons of the upstream gene *EPCAM* (*TACSTD2*). This deletion disrupts the transcription termination signal from *EPCAM*, resulting in read-through into *MSH2*. This results in methylation of the *MSH2* gene particularly in epithelial tissues where *EPCAM* expression is upregulated, causing a mosaic somatic methylation pattern (Kovacs et al. 2009). The risk of endometrial cancer in *EPCAM* deletion carriers appears to be significantly lower than in carriers of *MSH2* mutations, although the risk of colorectal cancer is comparable (Lightenberg et al. 2013).

Heterozygous cells repair DNA normally in Lynch syndrome (or at levels that generally do not have clinical consequences), but in cells where the second allele has been inactivated, for instance, by deletion, in the colonic epithelium, a mutator phenotype is generated and MSI is seen. Genes with microsatellite sequences in their coding regions (such as *TGFBR2*) are prone to somatic mutation, which is thought to promote the carcinogenic progression (de la Chapelle 2004). It has been suggested that the DNA MMR defect in Lynch syndrome generates increased numbers of novel and potentially immunogenic mutations, which result in an increased immunologic response to tumors in affected individuals. MSI can be demonstrated in hyperplastic endometrium in women without Lynch syndrome, but not in normal endometrium, and is also detectable in about 20 % of endometrial cancers (Baldinu et al. 2002). Similar findings have been described in individuals with Lynch syndrome with colorectal cancer and also even before the diagnosis of cancer.

### ***Extracolonic Cancer in Lynch Syndrome*** **(See also Endometrial Cancer, p. 102)**

Endometrial cancer is the fifth most common cancer in women in the UK, accounting for 7 % of invasive cancers in women, occurring in 1 in 100 women by 75 years of age. The commonest histological type (90 %) is adenocarcinoma (see p. 102).

Women with Lynch syndrome have a very high lifetime risk of endometrial cancer. Tumors characteristically demonstrate MSI+ (due to impaired repair of mismatch DNA errors), and complex atypical endometrial hyperplasia appears to be the premalignant endometrial lesion (Lohse et al. 2002; Sutter et al. 2004). Carriers of *MSH6* mutations have the highest endometrial cancer risk (Wijnen et al. 1999), and the risk is higher in *MSH2* than *MLH1* mutation carriers (Vasen et al. 2001; Huang et al. 2004). Women with Lynch syndrome have a lifetime risk of endometrial cancer of up to 60 %, with the highest incidence between 40 and 60 years of age, average 49.3 years. The characteristics of endometrial cancer in Lynch syndrome, which appear to be different from sporadic cancers, include more poorly differentiated histology (83 % versus 27 % in sporadic cancers) with Crohn's-like lymphoid reaction (100 % versus 27 %), lymphangio-invasive growth (67 % versus 0 %), and tumor invasion by lymphocytes (100 % versus 36 %) (Van den Bos et al. 2004).

The risk of ovarian cancer in women with Lynch syndrome is about 8% (see p. 107), highest in *MLH1* and *MSH2* mutation carriers. There is an increased risk of pancreatic cancer in Lynch syndrome, RR of 8, with cumulative risk of 4 % by the age of 70 years (Kastrinos et al. 2009). It is still unclear whether the risk of breast cancer is increased in individuals with Lynch syndrome. An increased risk of breast cancer has been reported recently, and the tumors have been shown to be deficient in the relevant MMR protein, especially in *MLH1* mutation carriers (Engel et al. 2012; Barrow et al. 2009; Jensen et al. 2009), although other studies have failed to demonstrate an increased risk (Watson et al. 2008). More recent studies have again suggested that there is an increased risk for breast cancer in MMR mutation carriers (Win et al. 2012). Engel et al. (2012) reported a significantly increased risk of prostate cancer in Lynch syndrome (SIR 2.5 (1.4–4)), highest in *MSH2* mutation carriers, and similar small increases in risk were reported in two other studies (Grindedal et al. 2009; Barrow et al. 2012) (see p. 116). Immunohistochemistry showed loss of the relevant MMR gene protein in most tumors tested. There is an increased risk of urothelial cancer in Lynch syndrome (see p. 141). The risk of gastric cancer is also increased, with a lower age at diagnosis than in the general population; the risk appears to be higher in countries where the background risk of gastric cancer is high (p. 51).

## Screening

First-degree relatives of individuals affected by Lynch syndrome should be offered screening for colorectal cancer and possibly for other cancers seen in their family. Since colorectal adenomas are assumed to be the premalignant lesions (for colorectal cancer), and the majority of lesions are right sided, colonoscopy is the screening method of choice (Hodgson et al. 1995; Vasen et al. 2007, 2013). Asymptomatic at-risk relatives (with an affected first-degree relative with Lynch syndrome) should be offered annual colonoscopy from the age of 25 (Umar et al. 2004b). Interval cancers have been detected in individuals screened at 2-yearly intervals, so annual

examinations are probably optimal but often not very practical, and therefore a “compromise” has been made by starting 18-monthly colonoscopies from 20 to 25 years of age, since fewer than 1 % of patients with Lynch syndrome develop colorectal cancer before the age of 20 years. The adenoma–carcinoma progression rate appears to be very much increased in Lynch syndrome above that in the general population (Jass 1995). If adenomas are found, they are removed, and colonoscopy should be repeated annually. There is good evidence that such screening does reduce cancer morbidity and mortality in screened individuals (Jarvinen et al. 1995; Renkonen-Sinisalo et al. 2000) and lead to the detection of CRC at an earlier stage, with a reduction of the risk of CRC by 63 %, and reduced colorectal cancer mortality (Vasen et al. 2007, 2013).

When colorectal cancer is detected in an affected individual, many centers advocate subtotal or even total colectomy because of the significant risk of a second colorectal cancer, but the evidence for and against such management options is still lacking, and there is currently a European trial to evaluate this (Olschwang et al. 2005). Prophylactic hysterectomy and subtotal colectomy may be considered in certain cases of Lynch syndrome (Celentano et al. 2011). Lifetime surveillance for rectal cancer should be continued after such surgery. The risk of rectal cancer has been assessed at 12 % over a 12-year follow-up period (Jarvinen et al. 2000). Such surgery could also be offered to MMR gene mutation carriers who have been found to have recurrent or dysplastic adenomas. Carrier women found to have colon cancer require careful preoperative assessment for ovarian and uterine cancer. Even if there is no evidence of current malignancy, prophylactic hysterectomy and bilateral oophorectomy at the time of colon surgery should be considered when there is a strong family history of these neoplasms. In view of the substantial risk of a second CRC after partial colectomy, the option of subtotal colectomy should be considered when undertaking surgery for a first colorectal cancer.

Aspirin significantly reduces the incidence of cancer in Lynch syndrome, so treatment with regular small doses may be advisable, but the pros and cons of such treatment should be carefully discussed in view of the side effects of such treatment.

It has been claimed that individuals with Lynch syndrome may have a survival benefit from treatment with adjuvant chemotherapy (Elsaleh et al. 2001), although the evidence for this is conflicting; current evidence suggests that tumors demonstrating MMR deficiency are resistant to chemotherapeutic agents including 5-FU, methylating agents, and antimetabolites (Bignami et al. 2003; Clark et al. 2004).

Because of the increased risk of gynecological cancers (ovarian and endometrial) in females with Lynch syndrome (possibly up to a half of total cancer risk), women with this disease and those at high risk of inheriting it should probably be followed up with annual bimanual pelvic examination and transvaginal ultrasound scan for ovarian and uterine cancers from 30 years of age. Transvaginal ultrasound with Doppler examination may delineate ovarian lesions, and a serum CA125 is also suggested annually (Jacobs and Lancaster 1996), but the efficacy of such surveillance is still unproven. Regular endometrial aspiration and biopsy (pipette or hysteroscopic biopsy) is more sensitive than ultrasound for the detection of premalignant lesions such as atypical endometrial hyperplasia and endometrial cancer (Wood and Duffy

2003), but since endometrial cancer has a relatively good prognosis, and the efficacy of surveillance is as yet unknown, screening would be best performed in the setting of a prospective study (Vasen et al. 1996, 2013) (see section on “Endometrial cancer”). Hysterectomy and bilateral oophorectomy largely prevent the development of endometrial and ovarian cancer and may be considered in women with Lynch syndrome after childbearing age, especially if colorectal cancer surgery is scheduled.

A high incidence of other Lynch syndrome-associated cancers in particular families may be an indication for screening for the specific cancer within that kindred showing an increased frequency of these extracolonic cancers. Thus, dermatological surveillance may be offered in Muir–Torre families. The estimated risk of urothelial cancer in Lynch syndrome varies from 5 to 20 %, highest in *MSH2* mutation carriers. These usually present with painless hematuria, and the prognosis is relatively good. Surveillance for urological malignancy could be offered by abdominal ultrasound and cytological examination of an early-morning urine sample for red blood cells and cytology, and tumor-specific markers, from 30 to 35 years of age, although this is controversial and not of proven efficacy (Myrhoj et al. 2008).

Most gastric cancers in Lynch syndrome are of the intestinal type, so regular upper GI endoscopy may lead to early detection of precursor lesions and early cancer. Precursor lesions have been ascertained in MMR gene mutation carriers: *H. pylori* infection was observed in 26 %, atrophy in 14 %, and intestinal metaplasia also in 14 % (Renkonen-Sinisalo et al. 2000). Gastrosopies annually, with eradication of *Helicobacter pylori* infection, when present, could therefore be considered from the age of 35 years in individuals with a strong family history of gastric cancer (Park et al. 2000) or those in areas with a high background risk of gastric cancer such as Japan, although the efficacy of such screening has not yet been established. (For more discussion see p. 61, Renkonen-Sinisalo et al. 2002; ten Kate et al. 2007; Vasen et al. 2007).

Because some studies have found a slight increase in the risk of prostate cancer in men with Lynch syndrome, screening by PSA analysis could be considered, but as no evidence exists for the benefits of screening for prostate cancer in MMR gene mutation carriers at the present time, this should only be considered as part of a research study (<http://impact-study.co.uk>).

Screening for pancreatic cancer has not been shown to be of benefit, so any surveillance should only be performed as part of a research study.

## ***Genetic Counseling in Lynch Syndrome***

Now that it is possible to delineate the mutation responsible for this disease in some families, it is possible to carry out predictive testing for the condition in families in which the pathogenic mutation has been detected in an affected individual. Such testing should only be offered with a full counseling protocol. Discussions should include providing information about the chances of developing cancer at a given age, and about the possible emotional effects of receiving a positive or a negative

result, and the potential implications with regard to insurance and employment (Aktan-Collan et al. 2000). Before using such molecular tests, it is important to be confident of the pathogenicity of the mutation by, for example, the demonstration that it segregates with the disease or has been shown to be pathogenic in other families, and that the nature of the mutation is likely to cause disruption of function.

The ascertainment and counseling of at-risk family members are of great importance and should be encouraged; there is often poor communication between different parts of a family. Genetic registers of families with this disease facilitate the follow-up of affected and at-risk individuals and the ascertainment of other individuals within a family who may benefit from screening (see screening for “Colorectal cancer”, p. 69).

### **Hyperparathyroidism–Jaw Tumor Syndrome (CDC73-Related Disorders) (OMIM 145001)**

Hyperparathyroidism–jaw tumor syndrome (HPT-JT) is an autosomal dominant disorder characterized by parathyroid adenoma or carcinoma, ossifying fibroma of the mandible and/or maxilla, and renal cysts, adenomas, and carcinomas. Germline mutations in *HRPT2*, currently known as *CDC73*, encoding parafibromin, are associated with HPT-JT (Carpten et al. 2002; Newey et al. 2010). Typically, HPT-JT patients present with solitary parathyroid adenomas or carcinomas. Rarely, they present with double neoplasias. Parathyroid carcinomas are extremely rare and are not components of any other heritable syndrome. So its presence should raise the genetic differential diagnosis of HPT-JT. Approximately 80 % of HPT-JT patients present with hyperparathyroidism (HPT). Parathyroid carcinoma, manifesting as primary hyperparathyroidism, occurs in approximately 10–15 % of affected individuals. A unique pathologic feature of parathyroid lesions in HPT-JT is the high frequency of cystic changes. About 30 % of patients also develop fibro-osseous lesions, primarily in the mandible and/or maxilla. Kidney lesions have been reported including bilateral cysts, renal adenoma, hamartomas, and papillary or chromophobe RCC. It is important to be aware that in some families, only parathyroid lesions are present (FIHP). Thus, HPT-JT (>50–80 % of patients), parathyroid carcinoma (20 % of all apparently sporadic cases), and familial isolated hyperparathyroidism (FIHP; 15 %) associated with germline mutations in *CDC73* are under the umbrella term *CDC73*-related disorders (Newey et al. 2010).

Germline mutations in *CDC73*, located on 1q25–q31, cause HPT-JT (Teh et al. 1996; Carpten et al. 2002). *CDC73* has 17 exons spanning 18.5 kb of genomic distance. HPT-JT-associated mutations are truncating, mainly (>80 %) frameshift and nonsense, with the majority occurring in exon 1 (Carpten et al. 2002; Newey et al. 2010). Recently, a germline large deletion in *CDC73* was reported (Cascon et al. 2011). Because this gene was recently identified, it remains unknown whether a genotype–phenotype association exists. The penetrance for HPT is 80 %, which mainly will develop by the late teens. The *CDC73* transcript is 2.7 kb and is

predicted to encode a 531-amino acid protein. While the gene is ubiquitously expressed, its function remained unknown for some time. Subsequently, parafibromin was shown to bind RNA Pol II as part of the PAF1 transcriptional regulatory complex (Yart et al. 2005) and importantly was found to mediate histone H3 K9 methylation which silences cyclin D1 expression (Yang et al. 2010).

Individuals and families who have or are suspected of having HPT-JT should be offered clinical cancer genetic consultation, which includes genetic counseling. When HPT-JT is suspected in a family or individual, DNA-based testing may be offered to establish the diagnosis and for medical management. Because *CDC73* has been identified, molecular-based differentiation of the various complex syndromes associated with hereditary primary HPT has become possible. Clinical surveillance and prophylactic maneuvers in HPT-JT are based on expert opinion. Annual blood-based biochemical tests for ionized calcium and intact parathyroid hormone levels beginning by or slightly after age 10 have been advocated. Following the example of multiple endocrine neoplasia type 1 (MEN 1), some believe that surgical intervention should occur once serum levels confirm the presence of HPT. Parathyroid disease in HPT-JT is typically asynchronous adenomas although the potential for malignancy needs to be seriously considered (Howell et al. 2003; Shattuck et al. 2003). While some groups advocate removal only of the enlarged parathyroid gland with continued regular monitoring, the alternative approach would be complete parathyroidectomy with fresh parathyroid autotransplantation to the forearm (or sternocleidomastoid) (Marx et al. 2002; Chen et al. 2003). Because of the unclear frequencies of jaw manifestations and renal neoplasias, it is unknown if surveillance for these component features would prove useful. The more aggressive among HPT-JT exponents would suggest orthopantomography of the jaw every 3 years as well as abdominal ultrasound or CT scan with and without contrast at least every 5 years after syndrome diagnosis to screen for polycystic disease, Wilms tumor or carcinoma, and renal hamartomas (Chen et al. 2003; Newey et al. 2010).

## Juvenile Polyposis Syndrome (JPS) (OMIM 174900)

Solitary juvenile intestinal polyps are relatively common in the pediatric population, occurring in approximately 1–5 %. A clinical diagnosis of juvenile polyposis syndrome (JPS) is made when multiple (>5) juvenile colonic polyps occur in any one individual (Waite and Eng 2003) or any number of juvenile polyps in an individual with a family history of juvenile polyposis. Despite its name, the age at diagnosis is bimodal, in childhood and in the mid-50s. JPS is an autosomal dominant hamartoma polyposis syndrome, often clinically diagnosed when other inherited hamartoma polyposis syndromes, such as PJS (see p. 299), Gorlin syndrome (see p. 252), BRRS (see p. 221), and hereditary mixed polyposis syndrome, have been excluded. The prevalence of JPS is believed to be 1 in 100 000. The number of polyps varies between individuals, even in the same family, but can be anywhere from 5 to 200. They are most often found in the lower bowel (98 %) but can also



develop in the stomach (15 %) and small intestine (7 %). Patients can become symptomatic from their polyps, with hematochezia, melena, rectal prolapse, intussusception, or abdominal pain. There is an increased lifetime risk for malignancy of 10–60 % for GI (colorectal, gastric, and duodenal) and possibly pancreatic cancer (Jass et al. 1988).

Histopathology plays a critical role in the diagnosis of JPS. The typical JPS polyp is unilobulated and pedunculated, spherical in shape with a smooth outer surface. In contrast to other hamartomatous polyps, these lack a smooth muscle core but instead show an internal dense inflammatory response, with predominant mesenchymal stroma that entraps normal epithelial cells, often forming dilated cysts. Less typical (20 %) are JPS polyps that are multilobulated, with each lobe separated by well-defined clefts (Jass et al. 1988).

As well as the colonic polyps, gastric polyposis may occur, often with quite large polyps, carrying the risk of GI bleeding and gastric cancer; gastric involvement is more common in individuals with *SMAD4* mutations than in those with *BMPRIA* mutations. Congenital anomalies have been reported in 11–20 % of individuals with JPS, more often in the sporadic cases (Coburn et al. 1995). These can involve the GI tract (including malrotation of the gut), heart, CNS, and genitourinary system. Clubbing of the fingertips is common, as is macrocephaly and congenital cardiac anomalies. JPS is associated with mutations in one of at least two genes. Germline mutations in *SMADH4* and *BMPRIA* have been found in approximately 40 % of JPS probands (Howe et al. 1998, 2001; Zhou et al. 2001). Germline mutations in *SMADH4* account for 15–25 % of JPS, while mutations in *BMPRIA* account for another 15–25 %. Both *SMADH4* and *BMPRIA* belong to the TGF beta superfamily. *BMPRIA* is phosphorylated by, and dimerises with, a specific type II BMP receptor. In turn, this activated complex signals through the intracellular SMAD1 or related SMAD5 and SMAD8 proteins, increasing their affinity for SMAD4, and gaining access to the nucleus for the transcriptional regulation of downstream target genes (Massague 2000; Eng 2001; Waite and Eng 2003). The prominent role of the BMP pathway in cardiac development and in the development of the GI tract might explain the association of some JPS with congenital cardiac anomalies and malrotation of the gut (Waite and Eng 2003). Further investigation might reveal cardiac anomalies predominating in those with *BMPRIA* mutations compared to those with *SMADH4* mutations. To date, the only genotype–phenotype correlation observed is the marked prevalence of giant gastric polyps in individuals with *SMADH4* mutations as compared to families with germline *BMPRIA* alterations (Friedl et al. 2002; Aretz et al. 2007). It is likely that there is at least one other JPS gene that has not been identified yet. While other members of the TGF–SMAD superfamily would be ideal candidates, no germline mutations in the genes encoding *SMAD1*, *SMAD2*, *SMAD3*, and *SMAD5* have been identified to date (Bevan et al. 1999), although a few cases of JPS have been ascribed to *ENG* mutations, with hereditary hemorrhagic telangiectasia (HHT). Features of HHT such as telangiectasia, epistaxis, and arteriovenous malformations can sometimes be seen in JPS, where the germline mutation is in *SMAD4* (reviewed in Gammon et al. 2009). While there were early reports of germline *PTEN* mutations in “JPS,” these were not confirmed as the individuals labeled as “JPS” either had features suggestive of Cowden syndrome or

were too young for the manifestations of Cowden syndrome to be apparent. Indeed, when a single hospital series of individuals given the diagnosis of JPS were analyzed for the presence of *PTEN* mutations, only one was found to harbor such a mutation, and he was subsequently found to have pathognomonic cutaneous features of CS (Kurose et al. 1999). A second study of 55 individuals in whom JPS has been diagnosed included only one with a germline *PTEN* mutation and Cowden syndrome (Waite and Eng 2003) or *PTEN* hamartoma tumor syndrome (PHTS). Clinical cancer genetic consultation, which includes genetic counseling, should be offered to all probands and families with JPS or suspected to have JPS. As with most inherited cancer syndromes with known susceptibility genes, the known affected individual should be tested for mutations in *SMADH4* and *BMPRIA*. Once the family-specific mutation is known, all first-degree relatives can be offered genetic testing in the setting of clinical cancer genetic consultation including genetic counseling. In such families, a mutation-negative result in a family member offered predictive testing is a true negative. An individual believed to have JPS and found to have a germline *PTEN* mutation should be informed he/she has PHTS or Cowden syndrome and medically managed as in CS (see p. 233).

Infantile JP is a rare subtype of JPS which presents before the age of two. It presents with rectal bleeding, intussusception, and diarrhea and may be fatal. It is usually sporadic, due to de novo mutations, such as contiguous deletions involving *BMPRIA* and *PTEN*.

## ***Clinical Surveillance***

Individuals with germline *SMADH4* or *BMPRIA* mutations should undergo upper and lower endoscopy from about 15 years of age to determine whether they have polyps at that time, whether these require further medical attention and to decide upon the interval of further endoscopies. In asymptomatic at-risk individuals, screening endoscopies should begin from 15 years age. Symptomatic individuals should have upper and lower endoscopies at the time of symptomatology. If no polyps are noted, then the screening interval may be every 2–3 years of age so long as the individuals remain asymptomatic. Suggested screening for individuals with juvenile polyposis is 18-monthly colonoscopies from the mid-teens and upper GI endoscopy from 25 years (Cairns et al. 2010), but because no large trials of such surveillance have been done, the evidence supporting this recommendation is limited.

When polyps are found, they should be removed, followed by an endoscopy at 1 year. When the tract is polyp-free, then screening intervals of 2–3 years can occur. If a JPS individual presents with nonmetastatic colorectal cancer, subtotal or total colectomy should be advocated at the time of surgery. Probands or families with the clinical diagnosis of JPS but are mutation negative at both *BMPRIA* and *SMADH4* should be managed as if they had mutation-proven JPS. Because large deletions and promoter mutations have not been systematically looked for in these 2 genes, it is possible that current “mutation-negative” JPS patients might harbor deletions and promoter mutations.

## Klinefelter Syndrome

In men, the incidence of cancer of the breast is about 1 % of the frequency in females. It has been estimated that about 3.8 % of males with breast cancer have Klinefelter syndrome, giving an extrapolated risk of breast cancer in males with the 47XXY karyotype of about 7 %. This is almost equivalent to the population risk of the disease in females to age 70 years. Studies vary in the extent of risk increase estimated: a relative risk of 5–49 in men has been estimated (Hasle et al. 1995; Swerdlow et al. 2005). There is an increased risk of breast cancer in males carrying mutations in *BRCA2*, but little data are available on the breast cancer risk in individuals with Klinefelter syndrome who carry such mutations.

Extragenital malignant germ cell tumors (teratomas, usually mediastinal, diagnosed before the age of 30 years) are significantly more prevalent in Klinefelter syndrome (relative risk 67), and any individual with early sexual development or testicular growth should be screened by measurement of germ cell tumor markers, including alpha-fetoprotein and human chorionic gonadotropin-B (Nichols 1992; Derenoncourt et al. 1995; Hasle et al. 1995; Ganslandt et al. 2000; Yong et al. 2000). Testicular tumors may be more common (perhaps secondary to cryptorchidism), and an association with AML and lymphoma has been proposed (Attard-Montalto et al. 1994), but this has not been substantiated (Machatschek et al. 2004) and may be due to the fact that cytogenetic studies are often performed in individuals with hematological malignancies (Hasle et al. 1995; Keung et al. 2002). A large study of the cancer risks in Klinefelter syndrome by the UK Clinical Cytogenetics Group found an increase in risk for breast (RR 5.2–49.2) and lung (RR 1–1.9) cancers and Hodgkin lymphoma (RR 0.8–3.9) and a reduction in risk of prostate (RR 0.02–0.7) cancer (Swerdlow et al. 2005).

The overall risk of cancer in Klinefelter syndrome is not substantially increased (RR 0.7–1.1), any increase being seen mainly in the age group 15–30 years of age, so that no routine cancer surveillance is recommended.

## Kostmann Syndrome (Kostmann Infantile Agranulocytosis, *SCN3*,) (OMIM #610738)

This is a rare autosomal recessive disorder characterized by granulocytopenia and monocytosis in infancy. There is an increased risk of myelodysplastic syndrome and/or AML in the severe congenital neutropenia syndromes, such that in follow-up study (mean 6 years), malignant transformation occurred in 10 % (Freedman et al. 2000). Neutropenia may respond to treatment with recombinant human granulocyte colony-stimulating factor. Recurrent homozygous mutations in the gene encoding HAX1, a mitochondrial protein implicated in preventing apoptosis in myeloid cells, have been identified in children with Kostmann syndrome (Klein et al. 2007). Other autosomal recessive severe congenital neutropenias

(SCN) are mainly caused by mutations in *ELA2*, encoding ELANE, the neutrophil elastase gene. This variety of SCN is sometimes referred to as SCN1 (OMIM #202700). Mutations in *GFII*, *WAS*, *CSF3R*, or *G6PC3* are also seen, but are much less common (Xia et al. 2009). More than a third of all cases of SCN remain unexplained.

## Li–Fraumeni Syndrome (OMIM #151623)

### *Clinical Features*

Li–Fraumeni syndrome (LFS) is a rare autosomal dominant disorder characterized by sarcoma, breast cancer, brain tumor, leukemia/lymphoma, and adrenocortical carcinoma (ACC) (Li and Fraumeni 1969; Li et al. 1988). Germline mutations in the *TP53* tumor suppressor gene on 17p13.1 have been found in approximately 70 % of LFS (Malkin et al. 1990; Srivastava et al. 1990; Varley et al. 1997). Deleterious *TP53* mutations leading to LFS occur in between 1 in 5,000 and 1 in 20,000 births.

The major component malignancies in LFS include sarcomas, breast cancer, brain tumors, ACC, and acute leukemia (Li and Fraumeni 1969; Garber et al. 1991; Li et al. 1991). Other associated cancers may include Wilms tumor; cancers of the colon, stomach, lung, and pancreas; as well as melanoma and gonadal germ cell tumors (Garber et al. 1991; Varley et al. 1997; Birch et al. 2001), although some of these are isolated observations in a single family, and so, their exact frequencies in mutation-positive individuals are unknown. The operational diagnostic criteria for LFS, the so-called classic criteria, are as follows (Li and Fraumeni 1969):

- An individual (index case) with a sarcoma diagnosed before age of 45 years
- A first-degree relative with any cancer before age of 45 years
- A third family member who is a first- or second-degree relative with either a sarcoma diagnosed at any age or any cancer diagnosed before age of 45 years

There are several sets of operational criteria for the diagnosis of LFS-like (LFL) families, such as the Eeles criteria (Eeles 1995) and the Manchester criteria (Varley 2003). The most recent set of criteria are the Chompret criteria, which have been recently modified (Tinat et al. 2009):

- Proband with tumor belonging to LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, brain tumor, premenopausal breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before age 46 years and at least one first- or second-degree relative with LFS tumor (except breast cancer if proband has breast cancer) before age 56 years or with multiple tumors
- Proband with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum and first of which occurred before age 46 years

- Patient with adrenocortical carcinoma or choroid plexus tumor, irrespective of family history

At least one of these three separate parts need to be fulfilled for the Chompret criteria to be fulfilled.

## Genetics

Germline *TP53* mutations cause LFS. In contrast to other cancer syndromes, missense mutations are the most common variety in LFS (Varley 2003; Ribeiro et al. 2001). Earlier studies had found that the mutation frequency in families meeting the standard clinical criteria for LFS is 70–80 % in most clinical laboratories (Varley et al. 1997; Friedl et al. 1999; Frebourg et al. 1995; Varley 2003). In families meeting the LFL criteria, the frequency is lower – 8 % using the Eeles criteria and 22–40 % using the Manchester criteria (Eng et al. 1997; Varley et al. 1997; Varley 2003; Birch et al. 1990, 1994). In a recent study, the classic criteria had high specificity (91 %) but low sensitivity (40 %), whereas the relaxed LFL criteria of Eeles were very sensitive (97 %) but not specific (16 %). The Chompret criteria offer the best compromise – 95 % sensitivity and 52 % specificity (Gonzalez et al. 2009).

The French LFS working group studied 474 French families suggestive of LFS, of which 232 fulfilled the Chompret criteria. Overall, they identified a germline mutation in 82 families (17 %). The percentage of positive results was much higher in those that met Chompret criteria (29 %) than in those that did not (6 %) (Bougeard et al. 2008). A more recent study added important details – among 525 patients sent to one US laboratory for testing, 17 % were positive for a germline *TP53* mutation. Notably, all positive cases had at least one family member with a sarcoma or breast, brain or adrenocortical carcinoma (ACC). All eight persons tested who had a choroid plexus tumor were positive for *TP53* mutations (Gonzalez et al. 2009). In contrast, others have found that about 50 % of children with choroid plexus carcinomas carry germline *TP53* mutations, and positive cases meet the classic criteria and had a very poor outcome. No cases that failed to meet the criteria carried germline mutations, and most had better outcomes. None of six children with a choroid plexus papilloma had a mutation (Tabori et al. 2010). As for ACC, 14 of 21 with a childhood ACC had a germline mutation, regardless of family history of cancer (Gonzalez et al. 2009).

Based on a segregation analysis of relatives of children with childhood sarcomas, the risk of cancer in LFS was estimated to be 50 % by age 30 years and 90 % by age 60 years. Molecular data have broadly confirmed these findings – the penetrance of *TP53* mutations for cancer is greater than 90 % for women (~75 % for men, the difference is mainly accounted for by high incidence of breast cancer diagnoses in women with LFS) (Chompret et al. 2000). Before age 10 years, the most commonly

seen cancers are soft tissue sarcomas, brain tumors, and ACC. For those 11–20 years, osteosarcomas predominate, and for those above 20 years of age, breast cancer and brain tumors are the most common manifestations, and all other epithelial tumors listed above tend to occur in those over age 20 years.

Genotype–phenotype correlations have been observed in some studies but not in others. For example, in one, families with missense mutations in the DNA-binding domain trended towards an overall higher cancer incidence, particularly of those of the breast and CNS, with an earlier age at onset, when compared to families with protein truncating or inactivating mutations or families with no mutation at all (Birch et al. 1998). Further, a systematic database study of all LFS families revealed that the mean age of breast cancer diagnosis in *TP53* mutation-positive families was 34.6 years in contrast to 42.5 years in mutation-negative families ( $P=0.0035$ ) (Olivier et al. 2003). In mutation-positive families, brain tumors were overrepresented in those families with missense mutations in the DNA-binding loop that contacts the minor groove of DNA. Development of ACCs was associated with missense mutations in the loops opposing the protein–DNA contact surface ( $P=0.0003$ ) (Olivier et al. 2003). In contrast, a study of 56 *TP53* mutation-positive individuals from 107 kindreds ascertained through cases of childhood soft tissue sarcoma reported no difference in phenotype between patients with missense mutations compared to those with truncating mutations (Hwang et al. 2003). Differences in patient accrual, study design, and mutation site classification may have contributed to these disparate findings, and thus more studies or a pooled analysis are needed to clarify this issue.

The frequency of germline *TP53* mutations in patients with multiple primary cancers unselected for family history and in those with apparently sporadic LFS component tumors has been extensively studied. While early studies suggested that only 1 % of early-onset breast cancer cases will harbor a germline *TP53* mutation (Sidransky et al. 1992; Lalloo et al. 2003), the frequencies may be higher in cases of sporadic osteosarcomas, 2–3 % (McIntyre et al. 1994), 9 % for rhabdomyosarcomas (Diller et al. 1995), and 2–10 % for brain tumors (Felix et al. 1995). Perhaps the most striking association occurs in cases of childhood ACC. In a series of 14 ACC patients unselected for family history, 11 (82 %) carried a germline *TP53* mutation (Gonzalez et al. 2009), and this is one reason why the Chompret criteria allow for ACC in the absence of family history (although it is fair to say that germline *TP53* mutations are very rare in those diagnosed over 20 years old). Interestingly of 36 cases of childhood ACC in southern Brazil, 35 carried an identical R337H (p. Arg337His) mutation. There is a single common origin for all carriers of the Brazilian R337H mutation (Pinto et al. 2004). The cancer family history in mutation-positive cases was not striking (there was no evidence for LFS in the 30 mutation-positive kindred), suggesting a low-penetrance and possibly tissue-specific effect of this particular mutation (Figueiredo et al. 2006). More recent data, however, have shown that other cancers can occur in R337H carriers (Gomes et al. 2012; Seidinger et al. 2011). Another recent development is the finding that most

LFS-related breast cancers are ER-positive, HER2-positive tumors (Wilson et al. 2010; Masciari et al. 2012). This may help in determining when to offer *TP53* testing to young women with breast cancer who do not meet classic or Chompret criteria, when generally the yield is low (Tinat et al. 2009).

## ***Genetic and Medical Management***

The management of LFS is not straightforward. Many are reluctant to offer predictive testing for minors in families with a known pathogenic *TP53* mutation in view of the difficulties in screening for such a wide spectrum of cancers in childhood without proven benefit from screening. However, it may be useful to view *TP53* mutation analysis as a molecular diagnostic test for LFS, especially in the setting of LFL. While breast cancer screening by MRI can be instituted, little effective surveillance is widely available for many of the other component tumors. On the other hand, most clinical cancer geneticists will acknowledge that a predictive test that is negative in the setting of a known family-specific germline *TP53* mutation can be useful. Such an informative negative test will relieve that particular family member from LFS-directed clinical surveillance as his/her cancer risk would be no different from that of the general population. Recently, a prospective study applying an intensive screening protocol originating at the Hospital for Sick Children, Toronto (see Table. 11.7), has provided some hope that aggressive screening can be of benefit, particularly in detecting small, operable brain tumors and in finding intra-abdominal tumors at a readable stage (Villani et al. 2011). Further large-scale studies with longer follow-up are required before this, or similar screening protocols can be accepted for wide-scale use (Table. 11.7).

## **Maffucci Syndrome (OMIM 166000)**

Maffucci syndrome (OMIM 166000) is a sporadic condition, in which osteochondromatosis (mostly enchondromas) and hemangiomas occur (in the related Ollier syndrome only cartilaginous tumors occur). Cavernous or capillary hemangiomas, phlebectasia, and lymphangiomas may develop and can be disfiguring. The dyschondroplasia may result in shortening of bones, fractures, and deformities from enchondromas. Many mesenchymal neoplasias may occur, possibly in 15–30 % of cases (Harris 1990; Albrechts and Rapini 1995). Chondrosarcoma is the most common malignancy to develop in this condition (75 %), but fibrosarcoma, angiosarcoma, osteosarcoma, ovarian granulosa cell tumors or teratomas, acute myeloid leukemia, and gliomas have been reported (Sun et al. 1985; Schwartz et al. 1987; Christian and Ballon 1990; Chang and Prados 1994). Multiple primary tumors may develop (Loewinger et al. 1977; Amary et al. 2011).

Maffucci syndrome was long suspected to result from constitutional mosaicism, and most cases are now known to be caused by mosaicism for specific



**Table 11.7** Surveillance strategy for individuals with germline TP53 mutations**Children***Adrenocortical carcinoma*

Ultrasound of abdomen and pelvis every 3–4 months

Complete urinalysis every 3–4 months

Blood tests every 4 months:  $\beta$ -human chorionic gonadotropin, alpha-fetoprotein,  
17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione

*Brain tumour*

Annual brain MRI

*Soft tissue and bone sarcoma*

Annual rapid total body MRI

*Leukaemia or lymphoma*

Blood test every 4 months: complete blood count erythrocyte sedimentation rate,  
lactate dehydrogenase

**Adults***Breast cancer*

Monthly breast self-examination starting at age 18 years

Clinical breast examination twice a year, starting at age 20–25 years, or 5–10 years  
before the earliest known breast cancer in the family

Annual mammography and breast MRI screening starting at age 20–25 years,  
or at earliest age of onset in the family

Consider risk-reducing bilateral mastectomy

*Brain tumour*

Annual brain MRI

*Soft tissue and bone sarcoma*

Annual rapid total body MRI

Ultrasound of abdomen and pelvis every 6 months

*Colon cancer*

Colonoscopy every 2 years, beginning at age 40 years, or 10 years before  
earliest known colon cancer in the family

*Melanoma*

Annual dermatological examination

*Leukaemia or lymphoma*

Complete blood count every 4 months

Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

Adapted with permission from Villani et al. (2011)

missense mutations in isocitrate dehydrogenase 1 (*IDH1*) or in *IDH2* (most commonly p.Arg132Cys substitution in *IDH1*) (Amary et al. 2011; Pansuriya et al. 2011).

**McCune–Albright Syndrome (OMIM 174800)**

McCune–Albright syndrome (MAS) is a nonheritable disorder classically characterized by the triad of polyostotic fibrous dysplasia (POFD), café-au-lait spots, and sexual precocity. Somatic gain-of-function mutations in the *GNAS1* locus on

20q13.2-q13.3 have been described in affected tissues. Since these mutations arise post-zygotically, affected individuals are considered somatic mosaics.

POFD is characterized by fibrous tissue proliferation with destruction of bone, leading to pathological fractures and pseudoarthroses. The diagnosis of McCune–Albright syndrome is usually clinically obvious and is confirmed by excess circulating levels of one or more hormones (thyroid hormone, cortisol, growth hormone, or estrogen) in the absence of the respective stimulating hormones. Fibrous dysplasia is usually diagnosed by its characteristic ground-glass (but occasionally sclerotic) appearance on X-ray, although it can be confused with osteofibrous dysplasia or hyperparathyroidism–jaw tumor syndrome (Hammami et al. 1997; Weinstein et al. 2002). Deafness and blindness may result from pressure within the cranial foramina. In addition, café-au-lait patches, with irregular borders, and multiple endocrinopathies occur. The most frequent endocrine disturbances are precocious puberty, especially in females, but thyroid dysfunction, hyperparathyroidism, acromegaly, Cushing syndrome, or hyperprolactinemia may occur. Osteosarcomatous transformation in areas of fibrous dysplasia has been described as a complication of this condition (Taconis 1988). Recently, four patients with severe McCune–Albright syndrome (two of whom had perioral freckling reminiscent of Peutz–Jeghers syndrome and three of whom had a detectable *GNAS1* mutation in peripheral blood) were found to harbor multiple hamartomatous gastrointestinal polyps in the stomach and/or duodenum. The authors suggested that gastrointestinal polyps may be frequent in patients with McCune–Albright syndrome (Zacharin et al. 2011).

It had been suggested that this disorder might be caused by somatic mutations in an autosomal dominant lethal gene, which would only be compatible with survival if present in mosaic form (Happle 1989). Subsequently, mutations in the *GNAS1* gene that encodes a subunit of the stimulatory G protein GS alpha were identified (Weinstein et al. 1991). It has been postulated that somatic mutations of this type occur early in embryogenesis and result in a mosaic population of cells, which would explain the sporadic occurrence and variable abnormalities in this syndrome (Marie et al. 1997). Subsequent to the initial description of somatic mosaic *GNAS1* mutations in this syndrome, alternative exons with multiple transcripts and imprinting were described (Weinstein et al. 2002; Rickard and Wilson 2003). Loss of exon 1A imprinting causes pseudohypoparathyroidism type Ib (Weinstein et al. 2002). *GNAS1* is biallelically expressed in most human tissues, but shows exclusive or preferential expression from the maternal allele in some tissues, including pituitary, thyroid, and ovary (Weinstein et al. 2002). In pituitary tumors that harbor an activating *GNAS1* mutation, the mutation almost always occurs on the maternal allele (Weinstein et al. 2002). Therefore the clinical manifestations observed in each McCune–Albright syndrome patient might be affected by which parental allele harbors the *GNAS1* gene mutation.

Since McCune–Albright syndrome and POFD result from somatic mosaic mutations, and not germline mutations, in *GNAS1*, these syndromes are virtually never inherited. Patients with fibrous dysplasia should not be treated with radiation, as it is ineffective and may increase the risk for malignant transformation. It would be prudent for all POFD patients to be screened for endocrine manifestations of McCune–Albright syndrome.

## Mosaic Variegated Aneuploidy Syndrome 1 (OMIM #257300)

The term mosaic variegated aneuploidy (MVA) was first used by Warburton and colleagues to describe a rare clinical entity associated with specific cytogenetic findings in cell lines (Warburton et al. 1991). The clinical picture is severe microcephaly, growth deficiency, mild physical abnormalities, and mental retardation. Many other features have been reported. Malignancies have also been found, with myelodysplasia, rhabdomyosarcoma, leukemia, and Wilms tumor reported. Cytogenetically, the main features are aneuploidy for different chromosomes occurring mosaically; the proportion of cells showing aneuploidy varies considerably, but often more than a quarter of all cells show aneuploidy. Based on these findings, it was postulated that the underlying molecular defect was homozygosity for an autosomal recessive gene mutation that predisposed to mitotic instability. Other cases of affected children whose parents were consanguineous supported this conjecture (Tolmie et al. 1988; Papi et al. 1989). It has been noted that in MVA 3 of 14 reported cases developed a malignancy (Jacquemont et al. 2002). The finding of homozygous mutations in *BUB1B* (Hanks et al. 2004) confirmed the earlier prediction and are of particular interest because of the associated cancer predisposition. Surprisingly, an adult male with multiple gastrointestinal tumors, including carcinoma of the ampulla of Vater, stomach, and colon, was found to be homozygous for a *BUB1B* mutation that created a de novo splice site (Rio Frio et al. 2010). It is likely that the attenuated phenotype observed was attributable to “leaky” splicing and a sufficient amount of functional normal BUBR1 protein being present.

*BUB1B* encodes BUBR1, a protein that is essential for mitosis. BUBR1 regulates the mitotic spindle. Somatic mutations in *BUB1B* are rare in most cancers studied thus far, but have been identified (Cahill et al. 1998), and genes that regulate mitosis are likely to have an important role in cancer (Lengauer et al. 1997). The question of whether cancers can arise solely from chromosomal instability has been debated (Rajagopalan et al. 2003; Sieber et al. 2003a, b). The recent findings in mosaic variegated aneuploidy and in clonal mosaicism (from genome sequencing studies) (Jacobs et al. 2012) support the notion that aneuploidy is a sufficient cause of carcinogenesis and perhaps suggest a bigger role for aneuploidy in cancer predisposition. Screening for cancer in patients with MVA is challenging, particularly in view of its rarity and very variable penetrance, and no studies of surveillance in individuals with this condition have been reported. In view of the identification of mutations in another gene in a variation of MVA, the original syndrome has been termed by some MVA1 (see below).

## Mosaic Variegated Aneuploidy Syndrome 2 (OMIM #614114)

A variant of MVA, currently referred to as MVA2 (MVA syndrome type 2), is caused by biallelic mutations in the gene encoding the centrosome protein CEP57, but no individuals with biallelic mutations in this gene have been reported to have been diagnosed with cancer (Snape et al. 2011), although so far, only 4 such cases have been reported overall.

## Multiple Endocrine Neoplasia Type 1 (OMIM 131100) and the *CDKN*-opathies

Multiple Endocrine Neoplasia Type 1 and *CDKN*-opathies also known as Wermer syndrome, is an autosomal dominant inherited cancer syndrome occurring in 1–2/100,000 live births and characterized by the classic triad of pituitary tumors, parathyroid neoplasia, and pancreatic endocrine neoplasia (Falchetti et al. 2010). Germline mutations in *MEN1*, encoding MENIN, on 11q13, are associated with MEN 1 (Larsson et al. 1988; Larsson and Friedman 1994; Chandrasekharappa et al. 1997; Thakker 2000).

### *Clinical Features*

The major endocrine features of MEN 1 are parathyroid tumors, typically hyperplasia (and not single adenomas), enteropancreatic endocrine tumors, and pituitary tumors, typically pituitary prolactinomas. As defined by the consensus diagnostic criteria, a diagnosis of MEN 1 is made in a person with 2 of the 3 major endocrine tumors. Familial MEN 1 is defined as at least one MEN 1 case plus at least one first-degree relative with 1 of these 3 tumors (Brandi et al. 1987; Falchetti et al. 2010). Primary HPT is the most common manifestation and, usually, the first sign of MEN 1, occurring in 80–100 % of all such patients (Falchetti et al. 2010). These tumors are typically multiglandular and often hyperplastic. The mean age at onset of MEN 1-related HPT is 30 years earlier in patients with MEN 1 than in the general population (20–25 years versus 50 years). Parathyroid carcinoma is not known to be associated with MEN 1, unlike in HPT-JT, the latter caused by mutations in the *HRPT2/CDC73* gene (see section on HPT-JT/*CDC73*-related disorders).

Pancreatic islet cell tumors, now referred to as neuroendocrine carcinomas of the pancreas, usually gastrinomas (manifesting as Zollinger–Ellison syndrome) and insulinomas, and less commonly VIPomas (vasoactive intestinal peptide), glucagonomas, and somatostatinomas, are the second most common endocrine manifestations, occurring in up to 30–80 % of patients by age of 40 years (Falchetti et al. 2010). These are usually multifocal and can arise in the pancreas or more commonly, as small (0.5 cm) foci throughout the duodenum. Gastrinomas represent over half of the pancreatic islet cell tumors in MEN 1 and are the major cause of morbidity and mortality in these patients (Skogseid et al. 1994; Norton et al. 1999; Brandi et al. 2001). Most result in peptic ulcer disease (Zollinger–Ellison syndrome), and half are malignant at the time of diagnosis (Weber et al. 1995; Norton et al. 1999). Nonfunctional tumors of the enteropancreas, some of which produce pancreatic polypeptide, are seen in 20 % of patients. Approximately 15–50 % of individuals with MEN 1 develop a pituitary tumor. Two-thirds are microadenomas ( $\leq 1.0$  cm in diameter) and the majority are prolactin-secreting (Corbetta et al. 1997). Other manifestations include carcinoids of the foregut (typically bronchial or

thymic, with the former more common in females and the latter in males), skin tumors including lipomas (30 %), facial angiomas (85 %), and collagenomas (70 %) (Skogseid et al. 1994) and adrenal cortical lesions, including cortical adenomas, diffuse or nodular hyperplasia, or rarely carcinoma (Falchetti et al. 2010). These adrenal lesions do not show loss of heterozygosity for the *MEN1* locus and might represent a secondary phenomenon (Skogseid et al. 1992; Burgess et al. 1996). Thyroid adenomas, pheochromocytoma (PC) (usually unilateral), collagenoma, facial angiofibroma, spinal ependymoma, leiomyoma, and melanoma have also been reported, but their frequency is not known (Falchetti et al. 2010).

## Genetics

Germline loss-of-function mutations in *MEN1*, on 11q13 and encoding MENIN, have been found in 80–90 % of MEN 1 probands belonging to families and approximately 65 % of nonfamilial probands (Larsson et al. 1988; Larsson and Friedman 1994; Chandrasekharappa et al. 1997; Falchetti et al. 2010). Exonic and whole gene deletions are found in another 1–4 % (Falchetti et al. 2010). Loss of the wild-type allele in many familial and sporadic MEN 1-associated tumors, as well as the fact that most mutations result in protein truncation, suggests that *MEN1* is a tumor suppressor gene.

Over 1,400 *MEN1* mutations have been reported to date, and like most tumor suppressor gene-associated loss-of-function mutations, they are nonsense, frame-shift, and missense and are scattered throughout the gene. Despite almost 15 years of investigation from the time of gene discovery, no genotype–phenotype associations are evident (Giraud et al. 1998; Wautot et al. 2002; Falchetti et al. 2010).

The protean role of MENIN is becoming clearer, and its localization to the nucleus and its interactions with proteins, chief of which is JUN-D, initially suggested that it may play a role in transcriptional regulation (Agarwal et al. 1999, 2003; Kim et al. 2003). While other MENIN partners such as NF-kappa-B, SMAD3, and REL-A have been described in vitro, it remains unclear whether these relationships hold in vivo. Subsequently, MENIN was shown to regulate H3 K4 methylation and expression of p18 and p27, a relationship which was corroborated by a knockout mouse model (Karnik et al. 2005; Scacheri et al. 2006). We now know that MENIN can bind DNA sequences throughout the genome, and the relationship of MENIN and epigenetic control is complex. It is interesting to know that wild-type, but not mutant, MENIN physically interacts with p53 and that overexpression of MENIN leads to gamma-irradiation-induced apoptosis, p21 expression, and proliferation inhibition (Bazzi et al. 2008). These observations do explain, at least partially, how MENIN can regulate proliferation and apoptosis in the endocrine cell through physical interactions with p53 (Bazzi et al. 2008). It is also possible that it plays a role in other regulatory pathways that lead to the control of cell growth and/or genomic integrity, but this remains to be seen.

## ***Genetic and Medical Management***

Individuals or families with MEN 1 or suspected of having MEN 1 should be referred for clinical cancer genetic consultation, which includes genetic counseling. The frequency of MEN 1 among patients with apparently sporadic component tumors varies but can be high for some tumor types. For instance, approximately one-third of patients with Zollinger–Ellison syndrome will have a clinical diagnosis of MEN 1 (Bardram and Stage 1985; Roy et al. 2001). Only 2–3 % of patients presenting with primary HPT have MEN 1 (Uchino et al. 2000), although familial isolated hyperparathyroidism (FIHP) is allelic (Pannett et al. 2003). In fact, 15 % of FIHP patients have been found to carry germline mutations in *CDC73* (see HPT-JT section). Other genetic differential diagnoses to consider in primary hyperparathyroidism include MEN 2 (see next section) and familial benign hypercalcemia caused by *CASR* mutations (Falchetti et al. 2010). Thus, germline *MEN1* mutation analysis can be a useful molecular diagnostic in the setting of apparently sporadic presentations of MEN1-component neoplasias. Finding a *MEN1* mutation is diagnostic of MEN1. Mutation analysis for *MEN1* and other genes, such as *HRPT2/CDC73*, can help differentiate MEN1 from HPT-JT in the setting of HPT presentation. HPT-JT also carries a risk for parathyroid carcinoma.

Among patients with pituitary tumors, the prevalence of MEN 1 is 2.5–5 % (Scheithauer et al. 1987; Corbetta et al. 1997), but is as high as 14 % in patients with prolactinoma (Corbetta et al. 1997). These results underscore the importance of carefully taking a thorough medical and family history in patients with a diagnosis of a MEN 1-associated endocrine tumor, even seemingly in isolation. Familial isolated pituitary somatotropinomas are rarely, if ever, due to germline *MEN1* mutations. Instead, 15 % of such familial isolated somatotropinomas are due to germline mutations in *AIP* encoding aryl hydrocarbon receptor-interacting protein (Vierimaa et al. 2006; Falchetti et al. 2010). Although germline *CDKN1B/p27* mutations have been reported to be associated with a MEN 1-like syndrome which includes pituitary tumors (Pellegata et al. 2006), a more recent systematic study did not reveal any *CDKN1B/p27* mutations (Agarwal et al. 2009). Involvement of genes in the CDKN/cyclin pathway is certainly in alignment given what we know of MENIN function (see above), but we suspect that the phenotypic spectrum of *CDKN1B* germline mutation is still evolving.

Approximately 25 % of Zollinger–Ellison syndrome is due to germline *MEN1* mutations (Falchetti et al. 2010). Thus, all such presentations should be referred to cancer genetic consultation for consideration of *MEN1* testing in the setting of genetic counseling. There are at least two reports of Zollinger–Ellison syndrome associated with germline mutations in the *CDKN1B/p27* gene (Agarwal et al. 2009).

The precise strategy for clinical surveillance of individuals with or at risk for MEN 1 remains controversial and based, for the most part, on expert opinion. The most aggressive surveillance protocols originate from Sweden, while the more

**Table 11.8** Sample surveillance program for patients with MEN 1 and asymptomatic MEN 1<sup>a</sup>


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For individuals known to have clinical MEN 1 or mutation in <i>MEN1</i>
<i>From age of 5 years</i>
1–2-yearly clinical examination and biochemical measurement of total serum calcium (corrected for albumin) and/or ionized calcium, fasting intact parathyroid hormone, prolactin
<i>Every 2–5 years from age of 15–20 years</i>
Upper abdominal CT or MRI scan
MRI scan of the pituitary with gadolinium contrast
MRI scan of the mediastinum in males
For individuals at 50 % risk of having clinical MEN 1 whose genetic status is unknown
<i>From age 5 years, annually</i>
Serum prolactin
<i>From age 10 years, annually</i>
Fasting total calcium (corrected for albumin) and/or ionized serum calcium
Fasting serum intact PTH
<i>From age 20 years, annually</i>
Fasting serum gastrin concentration if individual has symptoms of Zollinger–Ellison syndrome (reflux or diarrhea)

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<sup>a</sup>Mutation carriers (From Dreijerink and Lips 2005; Brandi et al. 2001; Falchetti et al. 2010)

conservative is from the USA and UK. As an illustration, a sample surveillance protocol is shown in Table 11.8 (Dreijerink and Lips 2005).

While surveillance, early diagnosis, and/or prevention form the mainstay of MEN 1 management, somatostatin analogues have been used to treat symptoms. Trials of anti-VEGF inhibitors and similar therapies are also being developed. Epigenetic modulation, given the role of MENIN, may be quite successful in the future.

## Multiple Endocrine Neoplasia Type 2 MEN 2 – OMIM 171400

MEN 2, also known as Sipple syndrome, is an autosomal dominant inherited cancer syndrome occurring in 1 in 300,000 live births and comprises three subtypes depending on the combination of clinical features (Schimke 1984; Zbuk and Eng 2007; Eng 2010). MEN 2A, the most common clinical subtype, is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PC), and hyperparathyroidism (HPT). MEN 2B, the least common subtype, is similar to MEN 2A except that component neoplasias occur earlier than that in MEN 2A, clinically apparent HPT is rarely, if ever, seen, and other features such as marfanoid habitus, ganglioneuromatosis of the mucosa, and medullated corneal nerve fibers are present (Gorlin et al. 1968). Familial MTC (FMTC) is characterized by MTC only in any given family (Farndon et al. 1986). Germline mutations in the *RET* proto-oncogene, on 10q11.2, have been found in 95 % of all MEN 2 probands (Eng et al. 1996a, b; Kloos et al. 2009).



### ***Multiple Endocrine Neoplasia Type 2A***

MTC is the most frequent complication of MEN 2A and occurs in more than 95 % of clinically affected patients. PC develops in about 50 % of patients, but there are interfamilial variations in predisposition, and the variations in frequency of PC have been correlated with specific *RET* mutations (Eng et al. 1996a, b; Zbuk and Eng 2007; Frank-Raue et al. 2011) (see below). Similarly, the incidence of HPT, which occurs in 15–30 % of patients, is also correlated with allelic variation (Eng et al. 1996a, b; Schuffenecker et al. 1998; Zbuk and Eng 2007). MTC is almost always the first manifestation of MEN 2A. Clinical epidemiologic studies suggested that about 25 % of all MTC presentations are MEN 2 and are characterized by C cell hyperplasia. MTC arise from these parafollicular C cells, which derive from the neural crest, and secrete calcitonin. Other hormones may also be secreted by this tumor, including adrenocorticotrophic hormone (ACTH), melanocyte-stimulating hormone (MSH), prolactin, serotonin, VIP, somatostatin, prostaglandins, and gastrin, so the symptomatology may be complex. About one-third of patients with MTC develop diarrhea, which resolves on removal of the thyroid gland. MEN 2A-related MTCs often present clinically between 20 and 40 years of age, and up to a quarter present with cervical lymphadenopathy. They may metastasize to liver, lungs, and bone. Over 90 % of MEN 2A-related PC are bilateral and multifocal, and occur, on average, about 8 years after MTC, with a mean age at diagnosis of 37 years (Howe et al. 1993), and are bilateral in approximately 50 % of affected patients. In the recent past, many believed that PC rarely precedes MTC, but population-based registries of PC have shown that germline *RET* mutations can be found in individuals with PC only (Neumann et al. 2002). However, extra-adrenal or malignant PC is infrequent in MEN 2. Up to 50 % of patients with PC are asymptomatic, and a rise in urinary catecholamines and vanillylmandelic acid (VMA) may be a late feature. Hypertension may develop, but paroxysmal hypertension, especially related to postural changes, is more typical of PC. An increase in the adrenaline–noradrenaline ratio in the urine may be noted earlier, as would serum chromogranin-A levels. Although clinical penetrance for MEN 2A is incomplete (approximately 45 % at age of 50 years and 60–75 % at age of 70 years), hyperplasia of thyroid C cells, which is the precursor of MTC, has a much earlier age at onset. C cell hyperplasia may be detected in asymptomatic mutation carriers by such biochemical screening tests and increases the apparent penetrance of MEN 2A to 93 % at age of 31 years (Easton et al. 1989).

### ***Multiple Endocrine Neoplasia Type 2B***

MEN 2B is similar to MEN 2A except that the mean age of tumor development in the former is an average 10 years earlier than the latter (Schimke 1984; Eng et al.

2001). Interestingly, clinically apparent HPT is rarely, if ever, observed in individuals with MEN 2B (Zbuk and Eng 2007; Kloos et al. 2009). Instead, they have characteristic stigmata including multiple mucosal neuromas and intestinal ganglioneuromatosis. There is a thin, asthenic marfanoid build, with some muscle wasting and possibly weakness. Joint laxity, kyphoscoliosis, pectus excavatum, pes cavus, and genu valgum are common. The face is elongated, the eyebrows are large and prominent, and the lips are enlarged and nodular, secondary to the neuromata – “blubbery” (Gorlin et al. 1968; Schimke 1984) (see Fig. 11.4). There may be multiple mucosal neuromas, which can be plexiform, and are visible on the eyelids, conjunctivae, and corneas. Enlarged corneal nerves (medullated corneal nerve fibers) may be seen. Cutaneous neuromas may also occur, and rarely, there may be café-au-lait patches and facial lentigines. The skin features may thus resemble those of NF 1, from which MEN 2B must be distinguished. Bowel malfunction, usually presenting with constipation or even obstruction, may result from ganglioneuromatosis of the gut (Carney et al. 1976). This must be distinguished from Hirschsprung’s disease (see below) and Cowden syndrome, where ganglioneuromatous polyps are common (Zbuk and Eng 2007; Heald et al. 2010).

MTC and PC develop in virtually all patients with MEN 2B. The tumors are bilateral and multicentric, and metastasize locally and distantly, often before the disease is recognized. MEN 2B-related MTC develop at a younger age (mean age at diagnosis, 20 years, often at very young ages) than MEN 2A and has been observed to be metastatic even before the age of 4 years (Wells et al. 1978; Eng et al. 2001; Kloos et al. 2009). While it is widely believed that the prognosis for MEN 2B-related MTC is worse than that in MEN 2A, well-controlled studies suggest that this is largely due to lead time bias.

### ***Familial Medullary Thyroid Carcinoma***

This is a relatively infrequent clinical subtype of MEN 2, believed to represent 5–10 % of all MEN 2 cases. FMTC is characterized by familial later-onset MTC without evidence of PC or HPT (Farndon et al. 1986). Given our current knowledge of the genetics of MEN 2, it is believed that FMTC and MEN 2A are artificially divided subtypes and may be on a continuum but representing phenotypes resulting from different penetrance (Zbuk and Eng 2007).

### ***Molecular Genetics of MEN 2***

The *MEN 2* locus was mapped to 10q11.2 and, subsequently, germline gain-of-function mutations in the *RET* proto-oncogene were found in probands with MEN 2A, MEN 2B, and FMTC (Gardner et al. 1993; Mulligan et al. 1993; Eng et al. 1994, 1995a, b; Bolino et al. 1995; Santoro et al. 1995; Zbuk and Eng 2007; Kloos et al. 2009).

Before the identification of *RET* as the MEN 2 susceptibility gene, the clinical penetrance of MEN 2A was said to be 70 % by the age of 70 years (Ponder et al. 1988). However, when molecular diagnosis became possible, the penetrance of MEN 2A when biochemical tests were used was found to be 100 % by the age of 70 years (Easton et al. 1989). Similarly, although early epidemiologic studies suggested that approximately 25 % of all MTC cases were due to MEN 2, when *RET* was identified, individuals with MTC tested without family history details or clinical details had a germline mutation frequency of approximately 25 % (Decker et al. 1995). Other studies have found frequencies ranging from 5 to 10 % (Eng et al. 1995; Wohlik et al. 1996; Schuffenecker et al. 1997; Wiench et al. 2001; Kloos et al. 2009). A population-based series of apparently sporadic PC, defined as no family history and no syndromic features, found a 5 % frequency of germline *RET* mutations (Neumann et al. 2002). Germline *RET* mutations have been identified in >95 % of all MEN 2, with 98 % of MEN 2A probands, 97 % in MEN 2B, and 85 % in FMTC (Eng et al. 1996a, b; Gimm et al. 1997; Smith et al. 1997; Kloos et al. 2009).

The characteristic mutational spectrum found in MEN 2A includes missense mutations in one of cysteine codons 609, 611, 618, 620 (exon 10), or 634 (exon 11) (Eng et al. 1996a, b; Kloos et al. 2009; Moline and Eng 2011). Approximately 85 % of MEN 2A individuals carry a codon 634 mutation (Eng et al. 1996a, b; Kloos et al. 2009; Moline and Eng 2011). Genotype–phenotype analyses reveal that codon 634 mutations are associated with the presence of PC and HPT (Eng et al. 1996a, b; Zbuk and Eng 2007; Kloos et al. 2009), and the C634R mutation is most often associated with the development of HPT (Mulligan et al. 1994; Eng et al. 1996a, b; Schuffenecker et al. 1998; Kloos et al. 2009). Rare “one-off” missense mutations seen in MEN 2A include those involving codons 630 and 790 (Eng et al. 1996a, b; Eng 1999), although the codons 790 and 791 mutations may be polymorphisms (Erlic et al. 2010). FMTC-associated mutations occur at the same cysteine codons as those in MEN 2A, although mutations at codons 609–620 are more frequent in FMTC than MEN 2A. The C634R mutation is associated with HPT, so FMTC families have C634Y and other 634 mutations (Eng et al. 1996a, b; Zbuk and Eng 2007; Kloos et al. 2009). Germline mutations found almost exclusively in FMTC include E768day (exon 13), V804L, and V804M (exon 14), although one family segregating V804L has been described with older-onset unilateral PC in 2 members (Eng et al. 1996a, b; Nilsson et al. 1999; Kloos et al. 2009). Germline M918T and A883F mutations occur in 95 and 2 %, respectively, of MEN 2B patients (Eng et al. 1996a, b; Gimm et al. 1997; Smith et al. 1997) and never in MEN 2A or FMTC. Interestingly, at least four MEN 2B patients appear to carry a V804M mutation in the presence of a *RET* variant of unknown significance (Miyauchi et al. 1999; Kloos et al. 2009).

Variable penetrance is apparent: *RET* codons 918, 883, and 634 mutations have the highest penetrance, predisposing to MEN 2B and MEN 2A with MTC, PC, and HPT involvement (Eng et al. 1996a, b; Eng 2000b; Kloos et al. 2009). Mutations at codons 609–620 have a broad range of penetrance and expressivity, with 50 % penetrance by the age of 36 years for MTC, 68 years for pheochromocytoma, and 82 years for HPT (Frank-Raue et al. 2011), and penetrance for MTC by 50 years ranged from 60 % for codon 611 mutations to 86 % for codon 620 mutations.

## ***Molecular-Based Medical Management in MEN 2***

*RET* testing in MEN 2 is considered the paradigm for the practice of clinical cancer genetics. Since *RET* mutations have been identified in >95 % of individuals with MEN 2, *RET* gene testing as a molecular diagnostic and predictive test is standard practice (Eng et al. 1996a, b, 2001; Kloos et al. 2009). In addition, all cases of MTC, irrespective of syndromic features or family history, should be offered *RET* gene testing in the setting of clinical cancer genetic consultation if possible.

In a MEN 2 family without a known mutation, *RET* testing should begin with an affected individual. Once a family-specific mutation is found, all at-risk family members should be offered testing before the age of 5 years in MEN 2A/ FMTC and before the age of 2 years, preferably within the first year, in MEN 2B (Kloos et al. 2009). For those individuals found to have a mutation, a prophylactic total thyroidectomy is recommended for all MEN 2 subtypes. This should be completed before the age of 5–6 years for MEN 2A/FMTC and before the age of 2 years, some believe 6 months, for MEN 2B (Wells et al. 1994; Kloos et al. 2009). The precise timing of prophylactic surgery remains controversial for FMTC, and in cases with codon 609, 768, and 804 mutations, which seem to have a lower penetrance and perhaps later onset of MTC (Eng et al. 1996a, b; Shannon et al. 1999; Frank-Raue et al. 2011), current ATA Guidelines suggest that prophylactic thyroidectomy can wait beyond age 5 if basal/stimulated calcitonins and neck ultrasounds are normal (Kloos et al. 2009). Clinical surveillance following thyroidectomy is dictated by what is found during the surgery. If the patient is found to have invasive MTC at the time of surgery, screening should include calcium-stimulated calcitonin testing every 3–6 months for the first 2 years, every 6 months from 3 to 5 years after surgery, and then annually. If only a small focus of MTC is found at the time of surgery, follow-up screening should involve annual basal (unstimulated) calcitonin for 5–10 years. If no cancer is present in the thyroid at the time of prophylactic surgery, no follow-up screening is indicated, even if C cell hyperplasia is present. All individuals who have undergone thyroidectomy need thyroid hormone replacement therapy and monitoring.

MEN 2-related PC almost always occurs after MTC. All mutation-positive individuals should undergo annual screening for PC beginning at 6 years. This usually consists of 24-h urine studies for VMA, metanephrines, and catecholamines. Some centers also advocate annual serum measurements for catecholamine levels and chromogranin-A. Abdominal ultrasound or CT/MRI scans for routine surveillance remains controversial.

In MEN 2, HPT is usually later onset and has age-related penetrance (Schuffenecker et al. 1998; Frank-Raue et al. 2011). Clinical surveillance in MEN 2A includes annual measurement of serum ionized calcium and intact parathyroid hormone levels beginning at the time of MEN 2 diagnosis. Once HPT is detected, removal of all four parathyroid glands is necessary. At that time or at the time of thyroidectomy, whichever occurs first, all glands and the thymus are removed. Half of the parathyroid gland should be pulverized and autografted into an easily accessible muscle of the arm or neck to control the body's calcium levels and can be

easily removed should HPT recur (Wells et al. 1994; Kloos et al. 2009). Since clinically evident HPT is rare in MEN 2B, parathyroid screening is not generally recommended for this subtype.

Management of *RET* mutation-negative MEN 2 families remains a conundrum. If there are sufficient clinically affected members in such families, linkage analysis using 10q11 markers within and around *RET* could be performed. In the event that the family is not large enough or informative for linkage, then management should follow that in the pre-*RET* testing era, and at-risk individuals should undergo annual screening for MTC (stimulated calcitonin screening), PC, and HPT from the age of 6–35 years. Prophylactic thyroidectomy is usually not routinely offered to this subgroup.

## Muir–Torre Syndrome (OMIM 158320)

Muir–Torre syndrome is a rare autosomal dominant condition, first described in 1967 in an individual who had multiple benign sebaceous adenomas and keratoacanthoma of the skin and multiple internal malignancies (large bowel, duodenum, and larynx) (Muir et al. 1967). The skin stigmata of this condition include sebaceous hyperplasia, adenoma, and carcinoma, with keratoacanthoma and basal cell cancer (BCC). The internal neoplasias include tumors of the colon, stomach and esophagus, breast, uterus, ovaries, bladder, and larynx and squamous cell carcinomas of the mucous membranes (Grignon et al. 1987). The syndrome is defined by dermatologists as a combination of at least one sebaceous gland tumor and a minimum of one internal malignancy (Cohen et al. 1991). The condition usually becomes manifest from the fifth decade of life, and multiple skin lesions develop.

It has become apparent that the main hereditary cause of Muir–Torre syndrome is mutations in the MMR genes *MSH2*, *MLH1* and *MSH6*. The presence of identical mutations in families with HNPCC/Lynch syndrome and Muir–Torre syndrome confirms that this syndrome is nearly always a variant of Lynch syndrome (Sieber et al. 2003a, b; Aretz et al. 2013; Bartkova et al. 2008; Kolodner et al. 1994) (but see note below on *MUTYH*-associated polyposis). The implication of this conclusion is that individuals with sebaceous carcinoma and a mutation in a MMR gene should be considered to be at an elevated lifetime risk of all the cancers that are known to occur in Lynch syndrome. In a large, single-institution study, 27 of 41 patients with Muir–Torre syndrome had mutations in *MLH1* or *MSH2* (Mangold et al. 2004). Interestingly, 25 of the 27 mutations were in *MSH2*, confirming multiple earlier observations that found far more mutations in *MSH2* than in *MLH1* (Lucci-Cordisco et al. 2003). Because the ascertainment criteria in the recent study of Mangold et al. were a sebaceous gland neoplasm and at least one internal neoplasm in the same patient (regardless of site of cancer or family history), it is not surprising that not all individuals with germline MMR gene mutations fell within the Bethesda guidelines for gene testing. Probably all sebaceous neoplasms occurring in the context of Muir–Torre syndrome are associated with MSI (Kruse et al. 2003), or loss of expression of *MSH2* (or rarely *MLH1* and *MSH6*) (Fiorentino et al. 2004), so all patients with sebaceous neoplasms should be offered either or both of these tests. If either

test suggests a MMR gene mutation, analysis should be carried out, even in the absence of an internal malignancy or a positive family history. The situation may be particularly challenging on the rare occasion when a child is diagnosed with a sebaceous neoplasm (which are usually periocular) (Omura et al. 2002); as in the absence of family history, testing of a minor may be warranted. From a laboratory standpoint, the spectrum of mutations in *MSH2* is similar to that seen in non-Muir–Torre-associated Lynch syndrome, no genotype–phenotype associations within *MSH2* are seen (Mangold et al. 2004), and a search for genomic deletions is indicated if sequenced-based analysis is negative (Barana et al. 2004).

Screening for cancer in relatives of individuals with this disorder is obviously important and should be similar to that outlined for Lynch syndrome, with extracolonic surveillance, particularly of the skin. It is interesting to note that in many families with Muir–Torre syndrome, only one person is affected by a sebaceous cancer, suggesting that other modifying factors may be present. In one Quebec family, which was later identified to carry a germline deletion in *MLH1*, the one person who developed sebaceous carcinoma only did so after receiving a heart transplant and subsequent immunosuppression (Paraf et al. 1995). The generality of this finding has been confirmed in a more recent study (Harwood et al. 2003).

When exposed to N-nitrosomethylbenzylamine, mice heterozygous for the gene encoding the fragile histidine triad gene, *Fhit*, developed a syndrome akin to human Muir–Torre syndrome (Fong et al. 2000). In human sebaceous carcinomas, *FHIT* protein was absent only from those tumors that were microsatellite stable, suggesting an alternative pathway to skin tumors in this syndrome (Holbach et al. 2002). No germline mutations in *FHIT* have been identified in Muir–Torre (or any other human cancer) syndrome. On the other hand, there have been reports of sebaceous carcinomas in *MUTYH*-associated polyposis (see below) and thus not all Muir–Torre syndrome is due to MMR gene mutations (Vogt et al. 2009).

## **MUTYH-Associated Polyposis (MAP) (OMIM 608456)**

Biallelic mutations in the *MUTYH* gene have been shown to be responsible for an autosomal recessive form of adenomatous polyposis. The *MUTYH* gene is involved in repair of oxidative DNA damage, and adenomas from affected patients show characteristic DNA repair errors. The number of colonic polyps in this condition tends to be between 15 and 200, significantly fewer than in classical FAP, although approximately 8 % of cases of polyposis with no detectable germline APC mutation, particularly cases with relatively few (100–500) polyps, have been found to carry biallelic mutations in the *MUTYH* gene (Sampson and Jones 2009). The disorder accounts for approximately 30 % of cases of attenuated polyposis, with 15–100 colonic adenomas; biallelic *MUTYH* mutations have been reported in 26–29 % of patients with 10–100 polyps and 7–29 % of patients with 100–1,000 polyps. Biallelic mutations have occasionally been reported in patients with fewer than 10 adenomas (Aretz et al. 2006; Brand et al. 2012; Al-Tassan et al. 2002; Sampson et al. 2003; Sieber et al. 2003a, b) and have been reported when a single colorectal cancer is the

sole phenotype (Lubbe et al. 2009). Duodenal adenomas are found in 17–25 % of individuals with MAP; the lifetime risk of duodenal cancer is about 4 %. Osteomas and CHRPE have also been reported in MAP patients (Sieber et al. 2003a, b; Bartkova et al. 2008; Aretz et al. 2013). An extended spectrum of tumor manifestations of biallelic mutations in *MUTYH* have been described (Vogt et al. 2009).

Management of patients with *MUTYH*-associated polyposis should be along the lines of FAP management, with upper GI surveillance, since affected individuals do have a risk of upper GI neoplasia. Screening should be initiated from the same age as recommended in AFAP (between 18 and 20 years). Because patients may develop only a few adenomas and CRC is often localized in the proximal colon, colonoscopy at 2-yearly intervals is preferable to sigmoidoscopy (Vasen et al. 2008).

Upper gastrointestinal endoscopy is advised, starting from 25 to 30 years of age, frequency depending on severity (Vasen et al. 2008). While this subject remains controversial, on balance, it seems that heterozygotes face little or no increased risk of GI polyps and colorectal cancer and do not require surveillance, but it is important to be certain that close relatives of affected individuals are offered genetic testing at least for the two common *MUTYH* mutations.

## N Syndrome (OMIM 310465)

This rare, X-linked recessive disorder was described in a single family (two affected brothers) and was characterized by mental retardation, chromosome breakage, and a predisposition to T cell leukemia. It is suggested to be caused by a mutation of DNA polymerase alpha (Floy et al. 1990).

## NAME Syndrome

See Carney Complex (above).

## Neurofibromatosis Type 1 (NF1) (Von Recklinghausen Disease, Peripheral NF) (OMIM 162200)

NF1 is the most common form of NF, with a prevalence of about 1 per 3,000 persons. Inheritance is autosomal dominant with variable expression, but approximately 50 % of cases represent new mutations. Characteristic clinical features are listed in Table 11.9. Conventional diagnostic criteria require two or more of the following features: (1) six or more café-au-lait lesions (more than 5 mm greatest diameter in children and more than 15 mm greatest diameter in adults); (2) two or more neurofibromas or one plexiform neurofibroma; (3) axillary or inguinal



**Table 11.9** Clinical features of NF1

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Neurofibromas
Café-au-lait spots
Axillary freckling
Lisch nodules
Intellectual impairment
Epilepsy
Macrocephaly
Short stature
Kyphoscoliosis
Pseudoarthrosis
Renal artery stenosis
<i>NS Neoplasia:</i> Optic glioma, astrocytoma and glioma, neurilemmomas, neurofibrosarcoma or malignant schwannomas
<i>Endocrine Neoplasia:</i> Pheochromocytoma, carcinoid
<i>Other Neoplasia:</i> Wilms' tumor, Rhabdomyosarcoma, Leukemia, Neuroblastoma

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freckling; (4) two or more Lisch nodules; (5) optic glioma; (6) characteristic osseous lesion (sphenoid dysplasia or cortical thinning of long bone, with or without pseudoarthrosis); and (7) a first-degree relative (parent, sibling, or child) with NF1 according to the above criteria.

The approximate frequencies of disabling nonneoplastic complications of NF1 were estimated by Huson et al. (1989) to be 33 % for intellectual handicap (3 % moderate–severe retardation, 30 % minimal retardation or learning difficulties), 5 % for scoliosis requiring surgery, 4 % for epilepsy, 2 % for severe pseudoarthrosis, and 2 % for renal artery stenosis. Café-au-lait spots occur in more than 99 % of patients with NF1 but are not specific and may fade in older patients (de Raed et al 2003).

The diagnosis of NF1 among at-risk relatives can usually be made early: Huson et al. (1989) found that all gene carriers have developed six or more café-au-lait spots by the age of 5 years, and 90 % of affected subjects have Lisch nodules by this age. Lisch nodules were reported to be present in 93–100 % of adults (aged over 20 years) with NF1 (Huson et al. 1989; Lubs et al. 1991; De Raed et al. 2003). Unlike café-au-lait spots and neurofibromas, multiple Lisch nodules are specific for NF1 and have only been reported rarely in NF2. In addition, Lisch nodules frequently develop before neurofibromas (Lubs et al. 1991), which, in the absence of molecular genetic testing, is very useful in the differentiation between minimally affected and unaffected individuals. In children with possible NF1 and no Lisch nodules, the ophthalmological assessment should be repeated periodically. Slit-lamp examination allows Lisch nodules to be distinguished from common iris nevi.

Individuals with NF1 are at increased risk of a variety of neoplastic lesions, including optic glioma, neurofibrosarcoma, brain gliomas, pheochromocytoma, and leukemia. Estimates of the increased risk of neoplasia are variable because of differences in the methods of ascertainment, and some older studies have not distinguished between NF1 and NF2. Sorensen et al. (1986) reported that the common perception

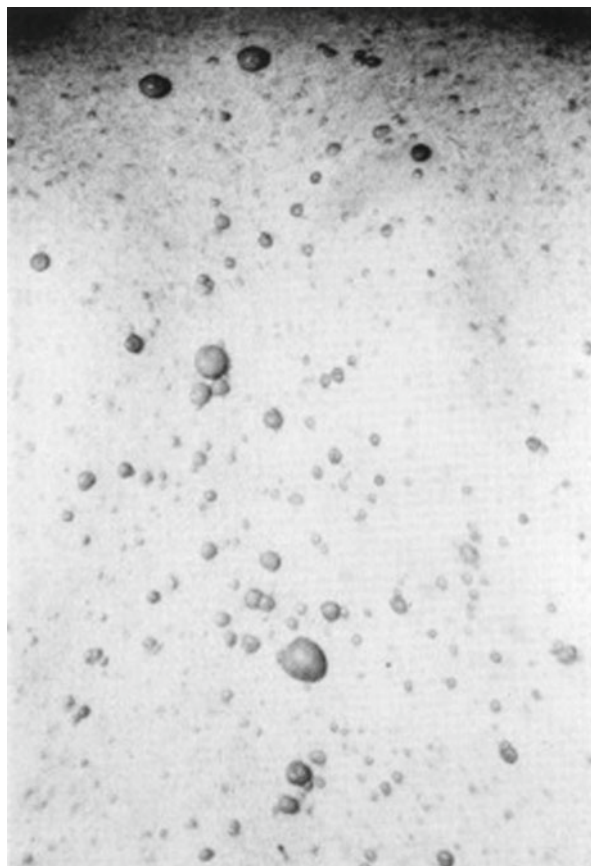
of NF as a severe disorder with greatly increased risk of cancer is incorrect. Although probands in a hospital-based study had a fourfold increase in the incidence of malignant neoplasms or benign CNS tumors, the relative risk among affected relatives was only 1.5 (0.9 in males, 1.9 in females). There was a significant excess of glioma, and although the relative risk of pheochromocytoma was greatly increased (because it is rare in the general population), the absolute risk was small. In a population-based study, Huson et al. (1989) estimated the overall risk of malignant or CNS tumors to be approximately 5 % (0.7 % for optic glioma, 0.7–1.5 % for other CNS tumors, 1.5 % for rhabdomyosarcoma, and 1.5 % for peripheral nerve malignancy). Endocrine tumors (pheochromocytomas, pancreatic apudomas) may occur in 3.1 %, and spinal and visceral neurofibromas each occur in about 2.1 % of patients. Stiller et al. (1994) reported a relative risk of chronic myelomonocytic leukemia of 221 in NF1, whereas the relative risks for acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma were 5.4 and 10, respectively. There is a small increase in the risk of breast cancer in women with NF1, and targeted early breast cancer screening has recently been suggested for these women (Evans 2012).

### *Specific Tumor Types in NF1*

Neurofibromas are benign tumors that usually involve the skin, although they can be subcutaneous or, rarely, visceral. Solitary neurofibromas may occur in an individual without a germline *NF1* mutation. The number of cutaneous neurofibromas increases with advancing age but shows wide variation (Huson et al. 1989) (Fig. 11.7). Two types of neurofibroma are distinguished: the common discrete variety in which the lesion arises from a single site along a peripheral nerve and has well-defined margins. Cutaneous neurofibromas are usually present in adults with NF1 and are most common on the trunk. About 20 % have head and neck lesions, and more than 100 neurofibromas are found in most older patients. Though cutaneous neurofibromas usually do not become apparent until puberty but can continue to increase in size and number throughout adulthood.

Plexiform neurofibromas are peripheral nerve tumors that extend along the nerve and can involve multiple nerve branches. Plexiform neurofibromas are often associated with local soft tissue overgrowth and, when the cranial nerves are involved, cause marked disfigurement. Plexiform neurofibromas appear as large, soft, subcutaneous swellings with ill-defined margins and may be present in about 25 % of NF1 patients (usually on the trunk), but facial involvement is rare (Huson et al. 1988). The principal complication of neurofibromas is cosmetic disfigurement, but there is also the risk of malignant change (malignant peripheral nerve sheath tumor, MPNST) (Evans et al. 2002; De Raedt et al. 2003). Malignant change is usually signaled by pain and rapid increase in size, and all patients should be alerted to the significance of these events. Plexiform neurofibroma is locally aggressive and may grow along the nerve of origin to involve the spinal cord or brain. The risk of malignant change was estimated to be 2–4 % (Huson et al. 1988), but a

**Fig. 11.7** Neurofibromatosis type 1. Dermal neurofibromata (Reproduced from the third edition, with permission from Cambridge University Press; Courtesy of Susan Huson)



population-based longitudinal study reported a lifetime risk of 8–13 % (median age at diagnosis 26 years) (Evans et al. [2002](#)).

Optic glioma is the most frequently reported CNS lesion in NF1, and about a third of children with optic glioma have NF1. Estimates of the incidence of optic glioma in NF1 patients vary: Huson et al. ([1988](#)) found in a population-based study that less than 2 % of patients with NF1 had a symptomatic glioma, but Lewis et al. ([1984](#)) observed a frequency of up to 15 % with routine cranial magnetic resonance imaging. Symptomatic optic gliomas usually present before 6 years of age. Histologically, optic gliomas are pilocytic astrocytomas, and these are generally nonprogressive tumors and are usually treated conservatively.

Other CNS gliomas reported in NF1 include brain stem gliomas, pilocytic astrocytomas of the hypothalamus and third ventricle, and, infrequently, diffuse gliomas of the cerebral hemispheres, cerebellum, or spinal cord. Although brain stem glioma may produce aqueduct stenosis and hydrocephalus, NF1 patients are also at risk for nonneoplastic lesions, such as dural ectasia and aqueduct stenosis without mass lesions.

NF1 is a well-recognized, but infrequent, cause of pheochromocytoma. The most frequent age at diagnosis of pheochromocytoma in NF1 patients is in the fifth decade (Walther et al. 1999b). Onset before the age of 20 years is uncommon, and this tumor is virtually unknown in childhood (Knudson and Strong 1972).

The other endocrine tumor that has been associated with NF1 is duodenal carcinoid. Typically, this is somatostatinoma with distinctive histological appearance (psammoma bodies) and somatostatin immunoreactivity (Griffiths et al. 1987; Swinburn et al. 1988). A variety of embryonal tumors have been reported in children with NF1, including rhabdomyosarcoma, Wilms tumor, and neuroblastoma (McKeen et al. 1978; Hartley et al. 1988). In addition, children with NF1 are predisposed to myeloid malignancies (200–500 times the normal risk), particularly juvenile myelomonocytic leukemia (Bader and Miller 1978; Clark and Hutter 1982).

The *NF1* gene maps to chromosome 17 and was identified in 1990 (Wallace et al. 1990; Viskochil et al. 1990). The *NF1* gene product (neurofibromin) is a negative regulator of Ras GTPase proteins, and the *NF1* gene appears to function as a classical tumor suppressor gene such that *NF1* wild-type allele loss has been detected in both malignant neurofibroma. *NF1* is a large gene (61 exons contained within 300 kb of DNA) and has a high mutation rate. De novo mutations usually arise in the paternal germline though microdeletions may be most often of maternal origin. Comprehensive mutation analysis can identify *NF1* mutations in >90 % of patients satisfying NIH diagnostic criteria (Boyd et al. 2009). Mutation analysis of the *NF1* gene is helpful in individuals who do not fulfill clinical diagnostic criteria or if prenatal or preimplantation diagnosis is being considered. Though in general the precise nature of an *NF1* mutation does not correlate with clinical phenotype, up to 5 % of cases have a complete *NF1* gene deletion which is associated with increased numbers of neurofibromas, more severe intellectual impairment, facial dysmorphisms, and increased risk of MPNST. Germline mutations in *SPRED1* cause Legius syndrome which is characterized by similar cutaneous findings to NF1 (multiple cafe-au-lait macules and axillary freckling) but not Lisch nodules or neurofibromas.

Patients with NF1 should be kept under surveillance, with annual clinical examination (every 2 years in children), but routine biochemical or radiological screening is probably not indicated in a service setting (Huson et al. 1988). The affection status for most at-risk relatives can be reliably established on clinical criteria because penetrance is close to 100 % for offspring of unequivocal cases (Riccardi and Lewis 1988). Although presymptomatic diagnoses of *NF1* by mutation analysis or linked DNA markers should be possible for most cases, it is not usually undertaken unless clinical diagnostic criteria are equivocal. Although detection of a *NF1* mutation might allow prenatal diagnosis, a limitation of molecular genetic testing is that the severity of the disorder usually cannot be predicted as NF1 characteristically has very wide variations in expression. Parents of apparently sporadic cases should undergo careful assessment for subclinical signs of NF1 (e.g., detailed skin examination with Wood's light and ophthalmological testing for Lisch nodules). Mosaic NF1 may be segmental, generalized (when disease is usually mild) or gonadal. Segmental mosaics present with localized cutaneous involvement (CALs/neurofibromas).

**Neurofibromatosis Type 2 (NF2) (Central Neurofibromatosis and Bilateral Acoustic Neuroma Neurofibromatosis) (OMIM 607379)**

NF2 is an autosomal dominantly inherited disorder estimated to have an incidence of about 1 in 33,000 persons per year and a prevalence of 1 in 55,000 (Evans et al. 2010). More than 50 % of cases have no family history of NF2 and result from de novo mutations. It has been estimated that about a third of patients are mosaic, and the NF2 mutation cannot be detected in blood (only in tumor tissue). NF2 accounts for 7 % of the patients with vestibular schwannomas (Evans et al. 2005). The hall-mark of NF2 is bilateral vestibular schwannomas (acoustic neuromas), but there is also a predisposition to other CNS tumors, such as meningioma, astrocytoma, ependymoma, and schwannomas of the dorsal spinal roots. NF1 and NF2 are distinct disorders, with the NF1 and NF2 genes mapping to chromosomes 17 and 22, respectively.

The clinical features of NF2 as reported by Evans et al. (1992, 1997; Eng et al. 2003; MacCollin et al. 2003) in a large UK study are shown in Table 11.10. Although peripheral neurofibromas may occur in NF2, they are rarely numerous, and Lisch nodules (iris hamartomas), axillary or groin freckling, and multiple (six or more) café-au-lait spots are not features of NF2. However, café-au-lait patches do occur in excess: Kanter et al. (1980) found that 61 % of NF2 patients had at least one café-au-lait spot or neurofibroma but that none had more than five, and Evans et al. (1992) found only one out of 97 patients had six café-au-lait patches. Glial tumors are less common than meningioma or schwannomas, and astrocytomas and ependymomas are usually low grade, affecting the lower brain stem or upper spinal cord. A mononeuropathy that occurs particularly in children and a generalized peripheral neuropathy that occurs in adults are increasingly recognized features of NF2 in some cases (Evans et al. 1992; Lloyd and Evans 2013).

The Manchester diagnostic criteria are widely used (see Table 11.11), but all clinical diagnostic criteria have a low sensitivity for diagnosing mosaic individuals without bilateral vestibular schwannomas and a family history.

**Table 11.10** Clinical features of NF2

Clinical features	Frequency (%)
Vestibular schwannoma	85
Meningioma	45
Spinal tumors	26
Skin tumors	68
Café-au-lait patch	43
Cataracts	38
Ependymoma	3
Astrocytoma	4
Optic sheath meningioma	4

Adapted from Evans et al. (1992)

**Table 11.11** Diagnostic criteria for NF2

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Bilateral vestibular schwannomas

Or

Family history of NF2 plus (a) unilateral vestibular schwannoma or (b) any two of meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular lenticular opacities

Or

Unilateral vestibular schwannoma plus any two of meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular opacities

Or

Multiple meningioma plus (a) unilateral vestibular schwannomas or (b) two or more of schwannoma, glioma, neurofibroma, or cataract

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The age of onset of NF2 is variable. Symptoms of vestibular schwannomas (usually hearing loss, which may be unilateral, sometimes vestibular disturbance or tinnitus) typically begin in the second or third decade (mean age of 23 years), but NF2 can present in the first or seventh decade (Kanter et al. 1980; Martuza and Eldridge 1988; Evans et al. 1992). Penetrance is more than 95 % at the age of 50 years, and the mean age at diagnosis is 28 years. The first manifestation of NF2 in some cases may be a congenital cataract. Some studies have suggested that there is an earlier age at onset in familial cases with maternal transmission (Kanter et al. 1980; Evans et al. 1992); however, there is no evidence of imprinting of the *NF2* gene, and this observation may result from a tendency for severely affected men not to have children.

The proportion of NF2 patients reported to have other non-acoustic CNS tumors is variable. Kanter et al. (1980) estimated it at 18 % and Evans et al. (1992) at 45 %, but studies of single families have shown a higher incidence. Higher frequencies may reflect more complete ascertainment through diagnosis of asymptomatic tumors and also interfamilial variations in predisposition to other non-acoustic CNS tumors. Meningiomas in NF2 are frequently multiple and may be intracranial or spinal.

NF2 has been subdivided into two forms, according to a mild phenotype (Gardner type) with late onset (above 25 years) and a more severe form (Wishart) with early onset and multiple meningiomas and spinal tumors. However, many cases do not fit neatly into either category (Baser et al. 2002b).

Individuals in the following categories should be evaluated for evidence of NF2 (Martuza and Eldridge 1988): (1) acoustic neuroma at age less than 30 years, (2) child with meningeal or Schwann cell tumor, (3) multiple CNS tumors with no diagnosed cause, and (4) adolescent or adult with one or more neurofibromas but no family history of NF1, no Lisch nodules, and only a few café-au-lait spots. A careful skin examination, ophthalmological assessment, and audiometry with brain stem auditory-evoked response should be performed initially, and an MRI brain scan (to detect acoustic neuroma and other intracranial tumors) should be arranged for those individuals with any abnormalities suggestive of NF2. Skin neurofibromas occur infrequently in NF2, but skin tumors should be carefully sought. The most common types of skin tumors are (1) discrete subcutaneous swellings appearing to arise from peripheral nerves and (2) well-circumscribed, slightly raised lesions with a roughened appearance and prominent hairs (Evans et al. 1992).



Relatives of affected people should be investigated for stigmata of NF2. Congenital cataracts should be sought by detailed ophthalmoscopy, and annual clinical examination (for evidence of cutaneous stigmata) should be performed during childhood. From the age of 10 years, annual audiometry and brain stem auditory-evoked potential should be performed (Evans et al. 1992). Skin and eye examinations are also indicated. A gadolinium-enhanced MRI scan is a sensitive investigation and, if available, performed annually from age 10. In many cases, surveillance will be continued until the age of 40 years, but the decision about when to discontinue screening will depend on the individual family. Although early diagnosis and surgery will prevent progressive neurological impairment, often hearing cannot be preserved. Affected patients should be prepared for the possibility of progressive hearing loss and warned to avoid heights and swimming alone. At-risk individuals demonstrated not to be gene carriers by molecular genetic analysis can be excluded from further surveillance.

A notable feature of NF2 is a high prevalence of somatic mosaicism such that up to a third of people with new mutations are mosaic (Kluwe et al. 2003; Moyhuddin et al. 2003). Mosaicism should be suspected in individuals with mild disease and no detectable *NF2* mutation in blood. In cases with bilateral tumors and no detectable mutation in blood, the identification of an identical *NF2* mutation in both vestibular schwannomas is an indication of mosaicism. The risk of disease transmission from mosaic parents to offspring is low when the constitutional *NF2* mutation cannot be identified in the parent blood using standard techniques, and somatic mosaicism can cause misleading results in linkage analysis for the second generation (such that individual predicted to be at high risk on linkage analysis may have inherited a wild-type allele) (Moyhuddin et al. 2003). Conversely children who inherit a *NF2* mutation from a mosaic parent will generally be more severely affected.

The gene for NF2 maps to chromosome 22 and was identified in 1993 (Rouleau et al. 1993; Trofatter et al. 1993). No evidence of significant locus heterogeneity has been reported for classical NF2, but familial schwannomatosis (p. 6) is caused by mutations in *SMARCB1*, and mutations in this gene have occasionally been seen in patients with unilateral vestibular schwannomas and multiple central and cutaneous schwannomas or multiple meningiomas and schwannomatosis (van Munckhof et al. 2012). Mutation analysis of *NF2* must include both sequencing and analysis to detect exon deletions. Identification of germline *NF2* mutations has provided genotype–phenotype correlations such that non-mosaic patients with nonsense or frameshift mutations generally have more severe disease (Wishart type) than those with missense or splice site mutations or large deletions (though some missense mutations may be associated with a severe phenotype) (Parry et al. 1996; Ruttledge et al. 1996). For non-VIII<sup>th</sup> nerve NF2-associated tumors (e.g., intracranial meningiomas, spinal tumors, and peripheral nerve tumors), people with constitutional *NF2* missense mutations, splice site mutations, large deletions, or somatic mosaicism had significantly fewer tumors than patients with nonsense or frameshift mutations (Baser et al. 2004; Selvanathan et al. 2010). Mosaicism is a further reason for phenotypic variability in NF2, and the high frequency of mosaicism influences molecular genetic investigation. Thus in cases of potential NF2 that fall short of the Manchester



diagnostic criteria, molecular genetic analysis of tumor material can be helpful in guiding whether the patient is mosaic for a *NF2* mutation, and detailed information relating to the age at diagnosis of vestibular schwannoma and risk of mosaicism and risks to relatives have been reported (Evans et al. 2012).

The prognosis of patients with *NF2* is influenced not only by genotype–phenotype correlations but also by surgical management with lower mortality in specialist centers (Baser et al. 2002a). Though surgery is the principal therapeutic intervention (with radiosurgery in some cases), there is increasing interest in the potential application of targeted nonsurgical treatments (Subbiah and Kurzrock 2012).

## Neurofibromatosis: Atypical

This group comprises forms of NF that do not neatly fall into the *NF1* or *NF2* categories. For example, in *NF3* there are features of *NF1* (café-au-lait spots, cutaneous neurofibromas characteristically on the palms of the hand) and of *NF2* (bilateral vestibular schwannomas, meningiomas, and spinal neurofibromas). Molecular genetic analysis of the *NF1* and *NF2* genes can be used to clarify the relationship of atypical forms of NF to *NF1* and *NF2*. Schwannomatosis, a variant of *NF2*, can have a distinct pathogenesis (see above).

## Nijmegen Breakage Syndrome, NBS (also known as Seemanova Syndrome II) (OMIM #251260)

This rare autosomal recessive disorder is characterized by microcephaly, growth retardation, “bird-like” face, premature ovarian failure, and humoral and cellular immunodeficiency. A characteristic feature is the marked discrepancy between the (usually) normal intelligence and severe microcephaly. The diagnosis of NBS is initially based on clinical manifestations and is confirmed by genetic analysis. There is very substantial risk of lymphoreticular malignancy – up to 50 % of patients develop lymphoma, at a median age of less than 11 years (Demuth and Digweed 2007). By age 20, 40 % of all NBS homozygotes have developed cancer (Chrzanowska et al. 2012). Laboratory findings include chromosome instability in cultured lymphocytes with frequent rearrangements involving chromosomes 7 and 14, cellular and chromosomal hypersensitivity to X-irradiation, and radio resistance of DNA replication (Taalman et al. 1989; Erola et al. 2003). Most reported cases are of eastern European (Slavic) origin, especially Czech Republic, Poland, western Russia, and the Ukraine, where a founder mutation (c.657\_661del5, p.K219fsX19, in exon 6) is common. The cellular phenotype chromosome breakage and immunodeficiency features of Nijmegen breakage syndrome and AT are similar, but the clinical phenotypes are distinct. The gene for Nijmegen breakage syndrome (*NBN*, formerly *NBS1*) encodes a protein (nibrin) (Varon et al. 1998) that is

phosphorylated by the ATM protein. Nibrin, together with *MRE11* and RAD50, forms a trimeric protein complex known as MRN that is involved in repairing DNA double-strand breaks. From studies of relatives of *NBN* homozygotes and from studies sequencing *NBN* in cancer cases and controls, it is clear that heterozygotes have an increased risk of tumors, including prostate and breast cancer, and melanoma (reviewed in Demuth and Digweed 2007).

## Noonan Syndrome (OMIM 163950) and the RASopathies

Noonan syndrome is characterized by cardiac defects, short stature, cryptorchidism, and characteristic facial features (ptosis, hypertelorism, a low hairline, and neck webbing). The most common cardiac defects seen (85–90 % overall) are pulmonary stenosis, hypertrophic cardiomyopathy, and VSD. 65 % may have a clotting defect. It affects approximately 1 in 2,500 people and was originally thought to be a variant of Turner's syndrome because neck webbing and short stature were features of both. However, the karyotype is normal in Noonan syndrome (NS), and it is inherited as an autosomal dominant trait. Mutations in *PTPN11* are found in about half of patients with this condition, and the gene product, SHP2, is a component of the mitogen-activated protein kinase (MAPK) signaling pathway. More recently, germline gain-of-function mutations in other genes involved in the same Ras/MPK pathway have been found in a proportion of cases, e.g., *SHOC2*, *KRAS*, *SOS1*, *NRAS*, *BRAF*, and *RAF1* (Pandit et al. 2006). Autosomal recessive Noonan syndrome may be caused by mutations in the *SHOC2* gene.

LEOPARD syndrome (LS) (OMIM 151100), so called because of its clinical features of lentigines, ECG anomalies, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, and deafness, is caused by gain-of-function mutations in *PTPN11* and therefore considered as a variant of Noonan syndrome (Tartaglia et al. 2006).

Germline mutations in other genes involved in the Ras/MPK pathway have been identified in children with related disorders, e.g., cardio-facio-cutaneous syndrome (CFC) (OMIM 115150) and Costello syndrome (OMIM 218040).

Preliminary studies have suggested that there is an increased risk of cancer in patients with Noonan syndrome with germline *PTPN11* mutations in older age groups, but this has not been confirmed. The main risk is for juvenile myelomonocytic leukemia. One mutation, threonine to isoleucine at position 73 in *SHP-2* (Thr73Ile), has been found in several NS patients suffering from JMML (Jongmans et al. 2011; Tartaglia et al. 2003).

CFC presents with cardiac defects, characteristic coarse facial features, hyperkeratotic skin lesions and nevi, sparse curly hair, sparse eyebrows, and severe developmental delay and is associated with germline mutations in *BRAF*, *KRAS*, *BRAF*, *MEK1*, or *MEK2* (Roberts et al. 2006), and Costello syndrome is characterized by cardiac defects, short stature, coarse facial features, and a significant increased risk of cancer, due to germline mutations in *HRAS* (Kerr et al. 2006).

It is thought that increased MAPK signal transduction results in cancer susceptibility; a germline *HRAS* mutation which encodes a p.G12V amino acid change with very high transforming potential causes severe neonatal lethal Costello syndrome. Most cases of Costello syndrome are due to a less strongly activating mutation p.G12S, which results in a 15 % lifetime risk of tumors. There is another recurrent mutation, p.G13C, which results in a milder phenotype. The lifetime risk of cancer in Costello syndrome is estimated to be 15 %, 60 % of these being rhabdomyosarcoma, which tend to occur in childhood, and others commonly being neuroblastoma and bladder cancer. The bladder cancer may occur as early as the second decade of life.

The risk of rhabdomyosarcoma in Costello syndrome is similar to that in Beckwith–Wiedemann syndrome, which may justify screening. Based on the recommendations for screening BWS patients, it has been suggested that children with Costello syndrome be offered screening by ultrasound examination of the abdomen and pelvis 3–6 monthly until 10 years of age for rhabdomyosarcoma and abdominal neuroblastoma, urine catecholamine metabolite analysis 6–12 monthly until 5 years of age for neuroblastoma, and annual urinalysis for hematuria for bladder carcinoma after 10 years of age (Gripp et al. 2002).

Noonan, CFC, and Costello syndromes, together with neurofibromatosis type 1 and Noonan syndrome with multiple lentigines (LEOPARD syndrome), caused by germline mutations in the genes in the Ras/MAPK pathway, are becoming known as the RASopathies, and a RASopathy patient/family support group has been proposed, but the patient groups remain separate as the issues are all rather different for the different conditions.

## Perlman Syndrome (OMIM 267000)

This rare disorder is an autosomal recessively inherited congenital overgrowth syndrome with phenotypic similarities to Beckwith–Wiedemann syndrome. Affected children are large at birth and hypotonic and have organomegaly, characteristic facial dysmorphisms (inverted V-shape upper lip, prominent forehead, deep set eyes, broad flat nasal bridge, low set ears), renal anomalies (nephromegaly and hydronephrosis), frequent neurodevelopmental delay, and high neonatal mortality (Perlman 1986; Greenberg et al. 1988). Perlman syndrome is associated with a very high risk of Wilms tumor (64 % incidence in infants surviving beyond the neonatal period), an earlier age at diagnosis than in sporadic cases (<2 years and 3–4 years, respectively), and a high frequency of bilateral tumors (55 %). Histological examination of the kidneys in children with Perlman syndrome shows frequent nephroblastomatosis (an important precursor lesion for Wilms tumor).

Perlman syndrome is caused by germline inactivating mutations in *DIS3L2* (a homologue of the yeast *Dis3* gene). Dis3 is a critical component of the evolutionarily conserved exosome complex, and it has been suggested that the inactivation of *DIS3L2* leads to disordered RNA metabolism with aberrant expression of mitotic checkpoint proteins (Astuti et al. 2012; Greenberg et al. 1986).

## **Peutz–Jeghers Syndrome (PJS)** **(OMIM 602216, OMIM 175200)**

PJS is a rare autosomal dominant inherited hamartoma cancer syndrome characterized by tiny pigmented mucocutaneous macules on the skin and GI hamartomatous polyps and a high risk of GI, breast, and pancreatic carcinomas (Hemminki et al. 1997; Eng et al. 2001). Germline mutations in *STK11* on chromosome 19p13 are found in most classical cases of PJS, but a very small proportion of cases do not have detectable mutations in this gene (de Leng et al. 2007; Volikos et al. 2006).

### ***Clinical Features***

The presence of melanin spots on the lips, perioral region, and buccal mucosa is pathognomonic for PJS and probably occurs in 95 % of such individuals (Peutz 1921; Jeghers et al. 1949). These tiny macules can also occur as black or bluish spots on the hands (especially the palms), arms, feet (especially plantar areas), legs, genitalia, and anus. The skin pigmentation is present from early childhood and may fade after the age of 25 years. The absence of the pigmented spots therefore does not exclude the diagnosis of PJS (Lampe et al. 2003). Most patients present because of symptomatology related to their GI hamartomatous polyps, although polyps can occur in the nasal mucosa, bladder, uterus, and gallbladder as well. They can present with episodes of colicky abdominal pain from childhood (usually the second decade). Intussusception and obstruction are not uncommon complications, and rectal bleeding, severe enough to present with anemia, may occur. The distribution of polyps is most commonly in the small intestine (60–90 %), but also in the colon (50–64 %), stomach (49 %), and rectum (32 %) (Jeghers et al. 1949). The polyps are broad-based hamartomas of the smooth muscle that extend into the lamina propria. Many show histological features of “pseudoinvasion.” Nevertheless, adenomatous change may develop within the polyps, and there is an increased risk of malignancy (relative risk 13), and mortality from cancer as high as 40 % by 50 years of age has been quoted for this condition (Boardman et al. 1998; Giardiello et al. 1987; Lim et al. 2004). In the absence of the characteristic melanin spots, the histopathology of the polyps is critical in making the diagnosis of PJS, as the PJS polyp has a diagnostically useful central core of smooth muscle that extends in a tree-like manner (“arborization”) into the superficial epithelial layer. There is frond-like elongated epithelium and cystic gland dilatation extending to the muscularis propria with arborizing smooth muscle. Thus invagination of the epithelial layer occurs, essentially trapping these cells within the smooth muscle component, and causing “pseudoinvasion” of the bowel wall that can be misdiagnosed as cancer, but has no evidence of cytological atypia. This involvement of the three tissue layers predisposes to intussusception and the formation of the distinctive lobulated PJS polyp. Nonetheless, the operational clinical diagnostic criteria for PJS are as follows:

1. Two or more histologically confirmed PJS polyps
2. Any number of PJS polyps or characteristic mucocutaneous pigmentation, with a positive family history of PJS
3. Any number of PJS polyps with characteristic mucocutaneous pigmentation (Aretz et al. 2005; Aaltonen et al. 1998)

In addition to an increased risk of GI cancer, extraintestinal cancers are overrepresented in PJS as well (Giardiello et al. 1987). Invasive ductal carcinomas of the breast and pancreatic adenocarcinomas are significantly associated with PJS (Boardman et al. 1998). Nonmalignant tumors associated with this syndrome include ovarian sex cord tumors and testicular (Sertoli cell) tumors. The histology of these tumors is intermediate between granulosa cell tumors and Sertoli cell tumors. They are common in this syndrome, and rarely malignant, although at least one such malignancy has been described. The clinical effects are mainly due to the hyperestrogenization in females and can give rise to adenoma malignum of the cervix, which can be very malignant. Many of these tumors occur in young adults, and the Sertoli and sex cord tumors may occur in prepubertal boys, causing sexual precocity and gynecomastia. Sertoli cell tumors of the ovary may occur, and ovarian sex cord tumors are common, bilateral and multifocal.

The relative risks of all cancers in PJS are high, assessed as 3 % by age of 30 years, 19 % by 40 years, 32 % by 50 years, 63 % by 60 years, and 81 % by age of 70 years. The respective risks of GI cancer (esophagus, stomach, small bowel, colorectum, and pancreas) are 1, 10, 18, 42, and 66 % and of gynecological cancer 3, 6, 13, and 13 % overall, and the breast cancer risks are 8 % by 40 years of age, 11 % by 50 years, and 32 % by 50 years of age. The risk of pancreatic cancer may reach 5 % by age 40 years and 8 % by 60 years (Lim et al. 2003, 2004).

## Genetics

Germline loss-of-function mutations in *STK11*, on19p13.3, encoding a multifunctional nuclear serine–threonine kinase, were found in a proportion of PJS individuals and kindreds (Hemminki et al. 1997, 1998; Jenne et al. 1998). *STK11* mutations have been found in 80–96 % of cases, leading to the suggestion of either locus heterogeneity or the presence of large deletions and promoter mutations, which have not been systematically analyzed. There is no clear genotype–phenotype association; current evidence suggests that it is unlikely that there is another major PJS locus.

*STK11* has nine exons, and the normal protein product acts as a tumor suppressor, a notable role for a protein kinase. Studies show that biallelic inactivation of *STK11* in the tumor, either through germline mutation plus somatic mutation or more commonly promoter hypermethylation of the wild-type allele, causes hamartomatous polyps to develop. The gene product is a serine–threonine kinase which regulates cell proliferation, partly via G1 cell-cycle arrest. It also plays a role in cell polarity and WNT signaling and is a negative regulator of mTOR in the TSC pathway.

## ***Genetic and Medical Management***

As with other inherited cancer syndromes, patients with or suspected to have PJS should be referred to clinical cancer genetic consultation. The presence of a germline *STK11* mutation is diagnostic of PJS. However, failure to find a mutation in an individual who meets the clinical diagnostic criteria for PJS does not exclude the diagnosis, and such individuals should be managed like anyone with PJS and/or germline *STK11* mutation.

Initial follow-up and management in PJS is aimed at detecting polyps in the bowel to prevent complications arising such as intussusception and intestinal obstruction. Later in adult life, screening is done to detect precancerous lesions and early cancer. Suggested protocols are baseline colonoscopy and upper GI endoscopy at 8 years and if no polyps are detected, initiating further small bowel video capsule endoscopies and colonoscopies at 18 years, 3 yearly. If polyps are detected at 8 years of age, 3-yearly screening is recommended from that age. It is also recommended that after the age of 50 years, the frequency is increased to every 12 months due to the rapid increase in cancer risk after this age. If video capsule endoscopies are not available, barium meal and follow-through in adults or MRI can be alternatives. If a laparotomy is being performed, endoscopic polypectomy (“on table enteroscopy and polypectomy”) should be considered. Screening for breast cancer by MRI annually from 25 years should be performed if possible, and cervical smears with liquid-based cytology are advised in adult women. However, screening for pancreatic or other cancers is not of proven benefit and is not recommended (Beggs et al. 2010). Treatment with MTOR inhibitors such as Rapamycin is under development with some initial indications of success.

Laparotomy may be required for suspicious symptoms. Polypectomy should be as complete as possible and can be performed at endoscopy. Surveillance for extraintestinal malignancy includes mammography, yearly gynecological evaluation and pelvic ultrasound, and 3-yearly cervical smears. Testicular ultrasound is suggested for males with feminizing features because of the risk of feminizing Sertoli cell tumors of the testis.

## **Pleuropulmonary Blastoma – Familial Tumor Dysplasia Syndrome (PPB-FTDS) (OMIM #601200, #138800)**

Pleuropulmonary blastoma (PPB) is a rare lung tumor which presents in children under the age of 72 months at one of three stages – type 1, a bland-looking, but malignant, cyst; type 2, a partly solid, partly cystic lesion; and type 3, an entirely solid, highly malignant sarcoma-like lesion (Priest et al. 1997). It is the sentinel lesion of the PPB-FTDS, also known as the DICER1 syndrome. Other characteristic features of this rare syndrome include lung cysts (essentially a quiescent or regressed form of PPB), multinodular goiter, ovarian sex cord–stromal tumors

(particularly Sertoli–Leydig cell tumor), cystic nephroma, embryonal rhabdomyosarcoma, and other very rare manifestations including pituitary blastoma, ciliary body medulloepithelioma, pineoblastoma, other primitive neuroectodermal tumors, juvenile intestinal polyps, adult-onset pleomorphic sarcoma, Wilms tumor, and possibly pulmonary sequestration (Priest et al. 1996; Hill et al. 2009; Foulkes et al. 2011; Rio Frio et al. 2011; Slade et al. 2011). Causative germline mutations in *DICER1*, a microRNA processing-RNase III-type endoribonuclease that is crucial for embryogenesis and early development (Bernstein et al. 2003), have been reported thus far in about 50 families (Hill et al. 2009; Bahubeshi et al. 2010; Foulkes et al. 2011; Rio Frio et al. 2011; Slade et al. 2011). Most of the germline mutations appear to truncate or otherwise disable the protein. In contrast, the second hits in the tumor, nearly all involve the RNase IIIb domain (Heravi-Moussavi et al. 2012) and apparently result in a failure to process 5' mature miRNAs (Gurtan et al. 2012).

## Porphyria

There are several forms of porphyria – inborn errors of porphyrin metabolism with sunlight-sensitive dermatological eruptions and abnormal porphyrin excretion patterns – most of which are inherited as autosomal dominant traits. Congenital erythropoietic porphyria is an autosomal recessive trait. Clinical and molecular aspects of the different porphyrias are reviewed by Kauppinen (2005). Siderosis of the liver develops in the hepatic porphyrias and can lead to inflammation and fibrosis, with the risk of hepatomas developing, particularly in porphyria cutanea tarda and variegate porphyria (Gisbert et al. 2004). The dermatological features of these two types are bullae and fragile skin in sun-exposed areas, with hyperpigmentation, hypertrichosis, photosensitivity, erosions, milia, and sclerodermoid areas. Treatment is by phlebotomy and chloroquine. Many of the genes underlying the porphyrias – notably coproporphyria, acute intermittent, erythropoietic, and variegate porphyria (Martasek et al. 1994; Ostasiewicz et al. 1995; Meissner et al. 1996) – have been delineated, and it is possible to detect germline mutations in these in affected probands. In a study of 650 patients with acute intermittent porphyria followed up for 7 years, 7 were diagnosed with hepatocellular cancer (3 asymptomatic), with an overall standardized rate ratio of 36 (95 % CI, 14–74). The occurrence of cancer was not related to the specific heme biosynthetic abnormality, but heme precursors were significantly increased (and melatonin decreased) in cancer cases (Andant et al. 2000). From a follow-up study of 39 patients with porphyria cutanea tarda on surveillance with 6-monthly ultrasound and CA125 measurements, on treatment with phlebotomies resulting in clinical remission, only one patient developed hepatocellular cancer (cumulative incidence 0.26 %), and this patient was an alcoholic with hepatitis C virus (HCV) infection (Gisbert et al. 2004). The authors concluded that the risk of hepatocellular carcinoma was relatively low in such patients, but that the risk increased with HCV infection and advanced fibrosis/cirrhosis. Other studies reported a relative risk of 5.3 (Fracanzani et al. 2001). It



has been recommended that PCT patients should have liver biopsies to determine the presence of such factors and surveillance if they were present. The percentage of hepatocellular cancer attributable to HCV infection may be 25 %, and most develop in cirrhotic livers; surveillance should be by 6-monthly screening in such high-risk patients (Montalto et al. 2002). Other genetic factors increasing the risk for hepatocellular cancer are hemochromatosis, glycogen storage diseases 1A and 1b, tyrosinemia, and alpha-1 antitrypsin deficiency (Dragani 2010) (see p. 53). Patients with porphyria should be checked for their hepatitis and hemochromatosis status as these likely increase the risk of neoplasia.

## **Rhabdoid Tumor Predisposition Syndrome 1 (OMIM #609322)**

Rhabdoid tumors are malignant, aggressive neoplasms that usually arise in infancy and early childhood. When these tumors occur in the brain and spinal cord, they are referred to as atypical teratoid/rhabdoid tumor (AT/RT), and when they arise in the kidney and/or soft tissues, they are termed malignant rhabdoid tumor (MRT) or extra-cranial rhabdoid tumor. Homozygous deletions on chromosome 22q, involving the *SNF5/INI1* gene (sucrose nonfermenting 5/integrase interactor 1), now known as *SMARCB1/BAF47*, were reported in cell lines derived from malignant rhabdoid tumors (Versteeg et al. 1998). The SMARCB1 protein and other family members such as BRG1/SMARCA4 (see below) and ARID1A/SMARCF1 are involved in chromatin remodeling (Wilson and Roberts 2011). Subsequently, germline mutations were identified in children with ATRT and MRT (Sevenet et al. 1999; Biegel et al. 1999; Taylor et al. 2000). One-third of children with ATRT/MRT carry germline *SMARCB1* mutations, and in about a quarter of cases, transmission from parent to child is reported, implying a less aggressive phenotype in the parent (Eaton et al. 2011). Compared to sporadic cases (untested or negative for *SMARCB1* mutations), familial cases, mostly with germline *SMARCB1* mutations, had earlier onset of more aggressive, widespread disease that was more likely to be fatal (Bruggers et al. 2011). An antibody to BAF47 (encoded by *SMARCB1*) is available and can be used as a screening step prior to germline mutation analysis, since *SMARCB1* appears to be a classical ‘two-hit’ tumor suppressor (Roberts and Biegel 2009). Germline *SMARCB1* mutations can also result in familial schwannomatosis, and occasionally, both ATRT and schwannomatosis have been reported in the same family (Carter et al. 2012).

## **Rhabdoid Tumor Predisposition Syndrome 2 (OMIM #613325)**

Investigation of two sisters with ATRT/MRT who did not show abnormal BAF47/SMARCB1/INI1 immunohistochemical staining or germline or somatic mutations in *SMARCB1* led to the identification of germline mutations in the partner molecule

BRG1/SMARCA4 (Schneppenheim et al. 2010). As for SMARCB1, immunohistochemical testing showed loss of BRG1/SMARCA4 in the tumor. The mutation was transmitted from an unaffected father. A second family containing a nine-month-old boy with an ATRT and a germline mutation in *SMARCA4* has also been reported (Hasselblatt et al. 2011). Therefore testing of *SMARCA4* might be indicated if the immunohistochemical staining of an ATRT/MRT for BAF47/INI1 is normal. The full spectrum of diseases associated with germline *SMARCA4* mutations remains to be determined.

## Rothmund–Thomson Syndrome (OMIM 268400)

This rare autosomal recessive disorder is characterized by atrophy, pigmentation, and telangiectasia of the skin associated with juvenile zonular cataracts and short stature. The dermal erythematous lesions may be present at birth and have usually appeared by the first 6 months of life. They begin on the face and spread to involve the whole of the body. The skin atrophy, pigmentation, and telangiectasia develop from the 3rd to the 6th month of life, particularly on extensor surfaces of the hands, arms, legs, and buttocks, and are worst over exposed surfaces. This inflammatory stage is followed by skin atrophy with pigmentation anomalies. Bilateral cataracts develop at 4–7 years, and there may be alopecia. Warty dyskeratosis is seen, and squamous cell carcinoma may develop in the skin in adulthood; multiple Bowen disease has been described (Haneke and Gutschmidt 1979; Kitao et al. 1999). There are two case reports of oral squamous cell carcinoma (Dahle et al. 2004). Associated abnormalities that may occur include sparse hair or alopecia, atrophic nails, microdontia or other dental malformations, hypogonadism, small saddle nose, hypoplastic thumbs, forearm reduction defects, small hands and feet, and osteoporosis or sclerosis.

Osteogenic sarcoma has been described in a proportion of patients (32 % in one series, mean age 11.5 years), and skin malignancy may also occur (Starr et al. 1985; Wang et al. 2001). Myelodysplasia and fibrosarcoma have also been described in this condition (Naryan et al. 2001). A subset of cases are due to biallelic mutations in the *RECQL4* helicase, and those with truncating mutations may be at higher risk of osteosarcoma (Wang et al. 2003a). In a 25-year retrospective study of 938 individuals with osteosarcoma, 66 had multiple primary cancers. One of these cases had Rothmund–Thompson syndrome, illustrating the rarity of this condition in patients ascertained by a diagnosis of osteosarcoma (Hauben et al. 2003).

Patients with Rothmund–Thompson syndrome have an increased risk of second malignant tumor – almost 20 % of Rothmund–Thompson syndrome patients being for a primary tumor (osteosarcoma, soft tissue sarcoma, or hematological neoplasia) developed a second malignancy (Stinco et al. 2008).

## Severe Combined Immunodeficiency Disease (OMIM 102700)

This comprises a heterogeneous group of disorders characterized by severe cell-mediated and humoral immunodeficiency. Autosomal recessive and X-linked forms (the most common form in males) occur. Although infection is the most common cause of death, there is also an increased risk of lymphoma (see p. 153). Following the mapping of X-linked severe combined immunodeficiency disease to Xq13.1, mutations in the interleukin-2 receptor chain gene were identified (Noguchi et al. 1993; Puck et al. 1993). Mutations are heterogeneous and molecular genetic analysis is technically demanding (Puck et al. 1997, 1997). An atypical form is also recognized. At least eight autosomal genes are implicated in recessive SCID including adenosine deaminase, CD3 delta and CD3 epsilon chain, CD45, IL-7 receptor alpha chain, JAK3 and RAG1/RAG2 deficiencies, and Artemis mutations (Buckley 2004a, b). There is no evidence that heterozygotes for autosomal recessive causes of the disease (including adenosine deaminase deficiency) are at increased risk for cancer (Morrell et al. 1987). A recent Australian survey of SCID recorded an incidence of 1.8 per 100,000 births. Of 33 cases identified over a 6-year period, 26 were classical SCID and 7 were atypical. Of the classical cases, the causative genes/syndromes were IL2RG ( $n=13$ ), ADA (4), IL-7 receptor alpha chain (1), Omenn syndrome (2), and DiGeorge syndrome (2), and 4 were autosomal recessive, not otherwise defined (Yee et al. 2008).

## Shwachman–Diamond Syndrome (OMIM 260400)

This is a rare autosomal recessive disease characterized by exocrine pancreatic insufficiency, skeletal abnormalities (e.g., metaphyseal dysostosis), growth retardation, recurrent infections, and hematological abnormalities (neutropenia, hypoplastic anemia, thrombocytopenia, or pancytopenia) (Dror and Freedman 1999) (see Table 11.12 for diagnostic criteria). The risk of leukemia in Shwachman–Diamond syndrome was calculated to increase 27-fold (Woods et al. 1981). A range of leukemic types have been described in this condition including ALL, AML, chronic myeloid leukemia (CML), and erythroleukemia. Although the risk of leukemic transformation had been considered to be 5–10 %, Smith et al. (1996) suggested that this was an underestimate. The Shwachman–Diamond syndrome gene maps to 7q11 and encodes a protein of 250 amino acids (Boocock et al. 2003). Most mutations appeared to result from gene conversion events with a pseudogene.

There is no apparent prognostic significance to genotype analysis. Patients with Shwachman–Diamond syndrome with very early symptoms or cytopenia at diagnosis are considered at a high risk of severe hematological complications (Donadieu et al. 2012). When comparing Shwachman–Diamond syndrome with other inherited bone marrow failure syndromes such as Diamond–Blackfan, Fanconi anemia, Kostmann syndrome, and dyskeratosis congenita, one of the main differences between

**Table 11.12** Diagnostic criteria for Shwachman–Diamond syndrome

Fulfilling at least two of the following criteria (1–4)	
1.	At least two of the following:
(a)	Chronic cytopenia(s) detected on at least two occasions over at least 3 months
(b)	Reduced marrow progenitors (granulocyte–monocyte colony-forming units, erythroid burst forming units, and granulocyte, erythroid, monocyte, megakaryocyte colony-forming units)
(c)	Persistent elevation of hemoglobin F (on at least two occasions over at least 3 months apart)
(d)	Persistent red blood cell macrocytosis (on at least two occasions over at least 3 months apart) (not caused by hemolysis or a nutritional deficiency)
2.	At least one of the following:
(a)	Evidence of pancreatic lipomatosis (e.g., by ultrasound, computed tomography, magnetic resonance imaging, or pathological examination of the pancreas e.g. by autopsy)
(b)	Reduced levels of at least two pancreatic enzymes adjusted to age (fecal elastase, serum trypsinogen, serum isoamylase, or duodenal enzymes following stimulation test)
3.	Positive genetic testing ( <i>SBDS</i> and others once they become available)
4.	First-degree family history of Shwachman–Diamond syndrome

Adapted from Hashmi et al. (2011)

Shwachman–Diamond syndrome and the other types of inherited bone marrow failures was that the combination of isolated neutropenia and high HbF or MCV was more likely to present at time of diagnosis in Shwachman–Diamond syndrome, whereas severe neutropenia and thrombocytopenia are less common at presentation (Hashmi et al. 2011).

## Simpson–Golabi–Behmel Syndrome (OMIM 312870)

An X-linked congenital overgrowth syndrome with some expression in carrier females, Simpson–Golabi–Behmel syndrome is characterized by prenatal and postnatal overgrowth, coarse facies with hypertelorism and a midline groove of the lower lip, and a variety of developmental defects including cleft lip and palate, polydactyly, supernumerary nipples, congenital heart disease, and cryptorchidism. Mental retardation is not usually a feature. Simpson–Golabi–Behmel syndrome must be distinguished from other overgrowth syndromes, in particular Beckwith–Wiedemann syndrome (BWS) (p. 221). There is an increased risk of embryonal tumors, and screening for Wilms tumor may be offered as described for BWS (renal ultrasonography every 3–4 months until age 7 years) (Scott et al. 2006).

Simpson–Golabi–Behmel syndrome is caused by mutations in the glypican 3 (*GPC3*) gene, which maps to Xq26 (Hughes-Benzie et al. 1996; Pilia et al. 1996; Brzustowicz et al. 1999). In addition, a second locus (*SGBS2*) was mapped to Xp22 in a family considered to have a severe form of Simpson–Golabi–Behmel syndrome, and a mutation in the *OFDI* gene was subsequently found in this family (making *SGBS2* allelic with oral–facial–digital type I syndrome) (Budny et al. 2006). Li et al. (2001) suggested that hepatoblastoma and nephroblastomatosis are part of the Simpson–Golabi–Behmel syndrome phenotype and identified *GPC3* deletion in two patients previously diagnosed as Sotos syndrome and Perlman syndrome.

## Sotos Syndrome (OMIM 117550)

The cardinal features of this congenital overgrowth disorder are a characteristic facial appearance (high and broad forehead, frontotemporal hair sparsity, and prominent chin), learning disability (mostly mild–moderate), and prenatal and childhood overgrowth (tall stature and macrocephaly). In most cases bone age is advanced. Neonatal jaundice and/or feeding difficulties are common. About 25 % of children will have congenital anomalies involving the heart (e.g., septal defects or more complex congenital heart defects), kidney (vesicoureteric reflux or structural anomalies), or spine (scoliosis) (Baujat and Cormier-Daire 2007; Tatton-Brown et al. 2007).

Sotos syndrome must be differentiated from other congenital overgrowth syndromes particularly Weaver syndrome but also Beckwith–Wiedemann syndrome, Bannayan–Riley–Ruvalcaba syndrome, and Simpson–Golabi–Behmel syndrome. A clinical diagnosis of Sotos syndrome can be confirmed by detecting inactivating mutations in the *NSDI* (nuclear receptor set domain protein-1) (Tatton-Brown et al. 2005). Most cases have intragenic *NSDI* mutations, but microdeletions can occur, and these are the most common cause of Sotos syndrome in cases from Japan. A few patients with Sotos-like features but no mutation in *NSDI* have been reported to harbor *NFIX* alterations (Yoneda et al. 2012). Most cases appear to be sporadic and arise from a de novo mutation, but familial cases are inherited in an autosomal dominant manner.

Although there is reported to be an increased relative risk of neural crest tumors and sacrococcygeal teratomas, the absolute risk of tumors has been estimated to be <3 %, and no specific screening is recommended (other than annual clinical review) (Tatton-Brown et al. 2007).

## Tuberous Sclerosis (Tuberose Sclerosis) (OMIM 191100 and 191092)

This is an autosomal dominant hamartomatous disorder with an incidence of approximately 1 per 12,000 live births. New mutations account for 70 % of cases, and the mutation rate is  $2.5 \times 10^{-5}$ /haploid genome. Most serious morbidity is caused by the CNS lesions, which produce mental retardation and epilepsy, but renal angiomyolipomas can occasionally be life threatening, and RCC may occur at an increased rate, albeit infrequently (Washecka and Hanna 1991). Tuberous sclerosis is a multisystem disorder and the clinical features are diverse (Lendvay and Marshall 2003):

**Skin:** Hypopigmented oval or “ash leaf” patches (80–90 %), facial angiofibromas (adenoma sebaceum, 40–90 %), Shagreen patches (20–40 %), forehead fibrous plaque (25 %), periungual fibromas (Koenen tumors) (15–50 %), and molluscum fibrosum pendulum (23 %).

*Eyes:* Hamartomas of the retina or optic nerve occur in about 50 % of patients with tuberous sclerosis. Just under half of these are calcified. Most retinal lesions do not grow, and although visual impairment from retinal or optic nerve astrocytoma is recorded, it is a rare complication (Robertson 1988).

*CNS:* Epilepsy (approximately 80 % of patients), mental retardation (50 %), and giant cell astrocytomas (5–10 %) are important features. Although MRI scanning demonstrates cortical tubers more easily than CT scanning, the latter is more sensitive in detecting small areas of intracranial calcification. Intracranial tumors are usually benign astrocytomas (subependymal nodules), which often calcify and are typically situated around the lateral aspects of the lateral ventricles. Infrequently, malignant giant cell astrocytomas develop from these subependymal nodules, most commonly near the foramen of Monro and resulting in bilateral (but often asymmetric) obstructive hydrocephalus. Less often, the tumor occurs at the frontal or temporal horns of the lateral ventricle or in the third ventricle. On CT scan, giant cell astrocytomas have a mixed pattern with foci of calcification and areas of vascularity showing enhancement with intravenous contrast. Most tumors are slow growing and distant metastases have not been reported. Subependymal giant cell astrocytomas can be demonstrated in about 8 % of patients, and although the proportion of tuberous sclerosis patients who develop intracranial hypertension is not accurately defined, it is estimated to be less than 3 % (Gomez 1988).

*Teeth:* Enamel “pits” due to enamel hypoplasia (70 %); however, these are very common in the general population and are not of any diagnostic value.

*Kidney:* Renal lesions occur in up to 75 % of cases and are a major cause of morbidity and mortality in older patients, and their importance has increased with the advent of more effective seizure control. The most frequent renal complications of tuberous sclerosis are angiomyolipomas (49 %) and renal cysts (32 %) (Cook et al. 1996). Angiomyolipomas are frequently multiple and bilateral. Most patients with a single angiomyolipoma do not have tuberous sclerosis, and patients with non-tuberous sclerosis-associated angiomyolipomas are usually middle-aged or elderly women (Robbins and Bernstein 1988). Angiomyolipomas in tuberous sclerosis patients present earlier (mean 32 versus 54 years) in non-tuberous sclerosis cases (Steiner et al. 1993). Most angiomyolipomas are asymptomatic, and although severe hemorrhage may occur, there is no indication to treat asymptomatic tumors. There is no convincing evidence for malignant transformation occurring in an angiomyolipoma (Robbins and Bernstein 1988). Angiomyolipomas consist of disorganized smooth muscle cells, adipose tissue, and aberrant blood vessels, which do not have an internal elastic lamina and are prone to rupture. Larger tumors tend to be symptomatic, and whereas small asymptomatic lesions may be kept under surveillance, it has been 1 that symptomatic angiomyolipomas  $\geq 4$  cm are investigated (angiography) and treated (embolization or renal sparing surgery). Renal cystic disease is the second most common renal manifestation, and renal cysts tend to occur at a younger age than angiomyolipomas. Severe renal cystic disease may result

from a contiguous deletion of the *TSC2* (see below) and *PKD1* (autosomal dominant adult-onset polycystic kidney disease) genes (Brook-Carter et al. 1994; Sampson et al. 1997).

The risk of RCC in tuberous sclerosis is controversial (Tello et al. 1998), but although it appears to affect only a minority of cases (2 %), those cases reported were frequently bilateral (43 %), with an early age at onset (median 28 years) (Washecka and Hanna 1991).

*GI:* Benign, small, adenomatous rectal polyps.

*Bones:* Cysts (60 %), areas of periosteal new bone/sclerosis (60 %). However, these findings are of no diagnostic value.

*Cardiac:* Rhabdomyomas are present in most infants with tuberous sclerosis. Thereafter many regress and echocardiographically demonstrable lesions occur in only about 30 % of adult patients. Obstructive symptoms or rhabdomyoma-induced arrhythmias are rare, and the likelihood of spontaneous regression favors conservative management in most cases.

*Lungs:* A specific feature of tuberous sclerosis is lymphangioleiomyomatosis (LAM) caused by an overgrowth of atypical smooth muscle cells. It is nearly always restricted to women and is very rare in the general population (1 per million) (Johnson and Tattersfield 2002) Honeycomb fibrosis is also seen but is rare.

Conventional diagnostic criteria for tuberous sclerosis are shown in Table 11.13. The manifestations of tuberous sclerosis can be mild and easily overlooked, so that the assessment of at-risk relatives must be performed assiduously. In addition to careful examination of the skin (including Wood's lamp examination) and nails, further examinations usually indicated include brain CT or MRI scans, renal ultrasound, specialist eye examination, and echocardiogram (in children). Dental pits are more common in patients with tuberous sclerosis, but their usefulness as a diagnostic feature is limited because many normal persons have small numbers of these. Truly non-penetrant gene carriers are extremely unusual, so that the risk to individuals with negative investigations as outlined above will be small. A frequent diagnostic problem occurs in assessing the significance of a single ambiguous lesion (e.g., ash leaf patch or equivocal CT scan finding) in an at-risk individual. Parents of a child with tuberous sclerosis who have been fully investigated with negative results should be given a 2 % recurrence risk for tuberous sclerosis in further children, because of the possibility of germline mosaicism or non-penetrance.

The presence of locus heterogeneity in tuberous sclerosis is firmly established, with two genes (*TSC1* and *TSC2*, respectively) mapped at 9q34 and 16p13.3 adjacent to the autosomal dominant polycystic kidney locus (APKD1). The *TSC2* gene was isolated first, and the *TSC1* gene was cloned 10 years after the initial mapping to chromosome 9 (van Slegtenhorst et al. 1997). Loss of heterozygosity at *TSC1* or *TSC2* is observed in hamartomas from tuberous sclerosis patients, consistent with both genes having a tumor suppressor function (Sepp et al. 1996). Half of familial cases are linked to *TSC1* and half to *TSC2*, but 80 % of sporadic cases have *TSC2* mutations (Jones et al. 1999). The proteins specified by the *TSC1* and *TSC2* genes



**Table 11.13** Diagnostic criteria for tuberous sclerosis. A diagnosis of tuberous sclerosis is suggested if a single primary or two secondary diagnostic features are present

Primary features	Secondary features
Classical shagreen patch	Ash leaf patch (hypomelanotic macules)
Ungual fibroma	Gingival fibroma
Retinal hamartoma	Bilateral polycystic kidney
Facial angiofibromas	Cardiac rhabdomyoma
Subependymal glial nodule (on CT scan)	Cortical tuber
	Radiographic “honeycomb” lungs
Renal angiomyolipoma	Infantile spasms
Lymphangioleiomyomatosis (lung)	Myoclonic, tonic, or atonic seizures
	First-degree relative with tuberous sclerosis
	Forehead fibrous plaque
	Giant cell astrocytoma

After Gomez (1988)

(hamartin and tuberin, respectively) interact directly with, and mutations affecting either gene result in the tuberous sclerosis phenotype (Hodges et al. 2001). Hamartin or tuberin inactivation leads to dysregulation of the mammalian target of rapamycin (mTOR) and abnormal cell growth (Inoki et al. 2005). This finding suggests that inhibitors of mTOR (e.g., rapamycin) have a potential role in tuberous sclerosis therapy.

Large kindreds with tuberous sclerosis are unusual, and in most cases reliable presymptomatic or prenatal diagnosis using linked DNA markers is not usually feasible. Molecular diagnosis by direct mutation analysis is possible, but the *TSC2* gene is very large and mutations are heterogeneous and so molecular diagnosis may not be available. All parents of apparently isolated cases of tuberous sclerosis should undergo detailed clinical examination (including examination of nails and Wood’s light), a CT or MRI brain scan, and renal and liver ultrasound examination. If these investigations are negative, the recurrence risk is reduced to approximately 2 %.

The clinical features of germline mutations in *TSC1* and *TSC2* appear similar, except that the presence of severe renal cystic disease is strongly correlated with deletions of both *TSC2* and *APKD1* genes (Brook-Carter et al. 1994), and intellectual disability is more frequent in sporadic cases, which are mostly caused by *TSC2* mutations. Renal carcinoma has been described in families linked to *TSC1* and to *TSC2*, and although RCC is uncommon in tuberous sclerosis, a germline mutation in rat *TSC2* gene is responsible for the Eker rat model of hereditary renal carcinoma (Kobayashi et al. 1995).

The investigation of asymptomatic at-risk relatives has been described. For unequivocally affected individuals, management is directed towards the active clinical problems; however, regular surveillance of asymptomatic angiomyolipomas may be undertaken, particularly if large (>4 cm). Symptomatic angiomyolipomas may be investigated by angiography and, particularly if larger than 4 cm. Diameter, embolization or renal sparing surgery performed.

## Turcot Syndrome (OMIM 276300 and 175100)

The association of multiple polyps of the colon with malignant tumors of the CNS is known as Turcot syndrome (Turcot et al. 1959). The condition seems to be rare. The colorectal polyps are characteristically not as numerous as in FAP (fewer than 100), and are larger, developing in the second decade of life, but the brain tumors may occur in childhood. Medulloblastomas and glioblastomas predominate. Café-au-lait spots and pigmented spots have been noted (Itoh and Ohsato 1985), and sebaceous cysts and BCC may occur (Michels and Stevens 1982).

Despite original suggestions that the condition was only an autosomal recessive trait, it is clearly autosomal dominant in some families (Costa et al. 1987; Kumar et al. 1989). Current evidence suggests that in some families, Turcot syndrome is allelic with FAP, especially where medulloblastomas predominate, and truncating germline *APC* mutations have been found in families with autosomal dominant Turcot syndrome (Hamilton et al. 1995). In other Turcot families (particularly those with glioblastomas), germline mismatch repair gene mutations have been reported (Tops et al. 1992; Liu et al. 1995). In these families, genomic instability was demonstrated in the brain and colonic tumors of affected individuals (Paraf et al. 1997). This has also been seen in normal tissue from patients with Turcot syndrome, perhaps suggesting that the single mutation in *PMS2* identified in this report was actually accompanied by another, hidden mutation (Miyaki et al. 1997). Clear evidence for autosomal recessive Turcot syndrome was provided by the report of two siblings who were diagnosed with a brain tumor and a colorectal cancer, respectively, at very young ages (De Rosa et al. 2000; Giunti et al. 2009). The authors identified two germline mutations in *PMS2* in the two children: 1221delG and 2361delCTTC, both of which were inherited from the patient's unaffected parents. A literature review of individuals with café-au-lait spots and early-onset colorectal cancer revealed excesses of early-onset brain tumors and lymphoma and/or leukemia. Several could be accounted for by homozygous mutations in *PMS2* or heterozygous mutations in *MLH1* (Trimbath et al. 2001a, b), and the condition is now known as constitutional mismatch repair deficiency syndrome (CMMRD), due to biallelic mutations in *MSH2*, *MLH1*, *MSH6*, and *PMS2* (p. 232). Other tumors have been reported in children with this condition including rhabdomyosarcoma and nephroblastomas; there is a suggestion that the MMR mutations causing this condition are less penetrant than those causing the usual type of Lynch syndrome because of the relatively low incidence of Lynch syndrome-type cancers in the families of affected children (Ostergaard et al. 2005; Giunti et al. 2009a, b).

Homozygous *PMS2* mutations occur in some children with brain tumors, but these cases are not strictly Turcot syndrome, as the supratentorial primitive neuroectodermal tumors (PNETs) that occur (along with café-au-lait lesions and susceptibility to hematological malignancies) (De Vos et al. 2004) are not usually associated with a personal or family history of colorectal cancer. However, De Vos et al. identified two germline *PMS2* mutations in the two siblings who were described by Turcot in 1959. Previously, a single *PMS2* mutation p.Arg134X had been identified in the two affected sibs and their father (Hamilton et al. 1995;

Trimbath et al. 2001), and although the parents were unaffected, it was assumed to be a dominantly inherited disorder in that family. The identification of another mutation, 2184delTC, and its presence in the mother, confirms the original Turcot pedigree as an example of autosomal recessive Turcot syndrome. This stresses the need for genomic analysis of *PMS2* in families with childhood supratentorial PNETs and/or other brain tumors, particularly if café-au-lait spots are present. Surveillance of first-degree relatives at risk for Turcot syndrome should include regular colonoscopies from age of 25 years in cases associated with Lynch syndrome or surveillance appropriate for FAP if this is the underlying condition.

## Turner Syndrome

Turner syndrome (TS) is due to complete or partial X-chromosome monosomy. The main risk of cancer in this syndrome is for gonadoblastoma, in cases with evidence of some Y chromosome lineage. However, the risk may only be 7–10 % and may have been overestimated in the past (Gravholt et al. 2000). The cumulative risk has been found to be 7.9 % by age 25 in this group of patients (Schoemaker et al. 2008). The risk of breast cancer is significantly decreased in TS (SIR 0.3 [0.2–0.6]). Tumors of the CNS, especially meningioma and childhood brain tumors, appear to occur with increased risk in TS (meningioma SIR 12.0 [4.8–24.8], childhood brain tumors 10.3 [2.1–30.1], cancers of the bladder and urethra 4.0 [1.3–9.2] and eye 10.5 [1.3–37.9]), and there may also be increased risks of melanoma, SIR 2.2 (95 % CI 1.0–4.4), and of corpus uteri cancer especially at ages 15–44 years (SIR 8.0 [1.6–23.2], compared with the general population, with a cumulative risk of 7.9 % (95 % CI 3.1–19.0) by age 25 years in this group (Schoemaker et al. 2008).

## Tylosis (Keratosis Palmaris et Plantaris) (OMIM 148500)

This autosomal dominant condition is characterized by a diffuse keratoderma of the palms and soles developing from the age of 5 years (typically around puberty). It is associated with a very high risk of developing cancer of the esophagus (95 % risk by the age of 60 years) (Harper et al. 1970). Oral leukoplakia also occurs and there is a risk of squamous carcinoma of the lip and mouth. The differential diagnosis from the more common diffuse palmoplantar keratoderma, which carries no increased risk of carcinoma of the esophagus, is that in the latter condition, lesions develop in infancy and are well established by 6–12 months of life. The incidence of esophageal cancer in gene carriers (heterozygotes) reaches 95 % by the age of 63 years, and the mean age at onset of the cancer is 45 years. Prophylactic esophagectomy with interposition of a segment of colon has been suggested for affected individuals. If prophylactic esophagectomy has not been performed, then annual esophagoscopy is recommended, and immediate esophagectomy is advisable if

dysplasia is detected. The gene for this condition has been mapped to chromosome 17q, but distal to the keratin gene cluster on 17q (Hennies et al. 1995; Kelsell et al. 1996), mutations of which are responsible for some forms of diffuse, focal, and epidermolytic palmoplantar keratosis. Finally, the tylosis gene itself was identified as *RHBDF2*. It encodes an inactive rhomboid protease (Blaydon et al. 2012).

A separate disorder of increased UVA sensitivity has been described, in which there is an autosomal dominant predisposition to the development of cutaneous pigmented keratoses in sun-exposed skin associated with the development of carcinoma of the uterus and other internal malignancies (clinically more apparent in females) (Atherton et al. 1989). Fibroblasts from affected individuals demonstrated an increased frequency of single-strand breaks in DNA following exposure to long-wave UVA.

## Von Hippel–Lindau Syndrome (OMIM 193300)

This is an autosomal dominant disorder with a minimal birth incidence of 1 per 35 000 (Maher et al. 1991). A wide variety of tumors have been reported in von Hippel–Lindau (VHL) disease, but the most frequent manifestations are retinal angioma (60 % of patients); cerebellar (60 %), spinal (13–44 %), and brain stem hemangioblastomas (18 %); renal cell carcinoma (RCC) (28 %); and pheochromocytoma (7–20 %) (Maher et al. 1990b; Maher and Yates 1991; Green et al. 1986). Renal, pancreatic, and epididymal cysts are also frequent findings. Other less frequent complications include pancreatic tumors (nonsecretory endocrine neuroectodermal tumors), endolymphatic sac tumors (ELST), and broad ligament cystadenoma (Maher et al. 2011). Clinical penetrance is age dependent and almost complete by the age of 60 years (0.19 at age of 15 years, 0.52 at 25 years, and 0.91 at 45 years). The mean age at clinical diagnosis is 26 years (though rarely retinal angiomas can present in infancy), and age at diagnosis of complications is earlier in at-risk relatives under routine surveillance (see later). There is a high probability of a patient with VHL disease developing a major complication (the risk lifetime risks of cerebellar hemangioblastoma, retinal angioma, and RCC are each >70 %) (Ong et al. 2007). Nevertheless, the expression of VHL disease is very variable, and, notably for pheochromocytoma, marked interfamilial variability also occurs.

Clinical diagnostic criteria for VHL disease are (1) for isolated cases, two or more hemangioblastomas (retinal or CNS) or a single hemangioblastoma in association with a visceral tumor or endolymphatic sac tumour (ELST) or (2) if there is a family history of retinal or CNS hemangioblastoma, only one hemangioblastoma, ELST, or visceral tumor is required for the diagnosis (small numbers of visceral cysts do not provide an unequivocal diagnosis in familial cases). Up to 20 % of probands represent *de novo* mutations, and diagnosis in isolated cases is often delayed because they are only recognized when two complications have developed (whereas familial cases can be diagnosed after a single manifestation).

Nevertheless, increasingly the diagnosis is made by molecular genetic analysis after screening of individuals with an isolated manifestation (e.g., hemangioblastoma, pheochromocytoma).

### ***Cerebellar Hemangioblastoma*** (See p. 4)

This is the joint most frequent complication (with retinal angiomas) of VHL disease. Approximately 30 % of cerebellar hemangioblastomas occur as part of VHL disease, and evidence of VHL disease should be sought in all patients with apparently sporadic cerebellar hemangioblastoma. Tumors complicating VHL disease occur, on average, at a younger age than sporadic cerebellar hemangioblastomas (see p. 4), and in about 20 % of cases the tumors are multiple or recurrent. CT scanning demonstrates a contrast-enhancing mass, but MRI scanning is more sensitive and is preferred – particularly for surveillance. These tumors are benign, may be cystic or solid, and the histological appearance is identical to that of a retinal angioma (hemangioblastoma). Approximately 4 % of patients with apparently sporadic cerebellar hemangioblastoma have a germline VHL gene mutation (Hes et al. 2000). In view of the risk of false-negative mutation analysis and somatic mosaicism, apparently sporadic early-onset cases may be kept under review in case evidence of VHL disease develops later. Surgery is usually performed when a hemangioblastoma becomes symptomatic. Stereotaxic radiotherapy may be occasionally an option for small non-cystic hemangioblastomas that are not amenable to standard surgery (Patrice et al. 1996).

### ***Spinal Cord Hemangioblastoma***

This is the second most frequent site for CNS hemangioblastomas. Pain is the most common symptom and may be followed by sensory loss and signs of cord compression. MRI scanning is the preferred method of investigation. Symptomatic lesions should be excised, and although the prognosis can be good, if diagnosis is delayed or surgery difficult, paraplegia may result. Medical treatment with anti-angiogenic agents may be considered if conventional surgery is not possible (though CNS tumors are less likely to respond than renal or pancreatic tumors).

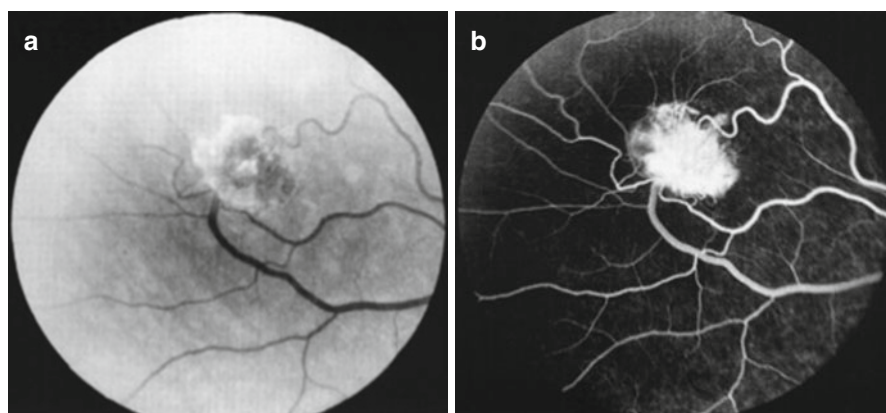
### ***Brain Stem Hemangioblastoma***

These are symptomatic in 18 % of patients, most often in the dorsal medulla and craniocervical junction (Filling-Katz et al. 1991). Supratentorial hemangioblastomas are rare. Many CNS hemangioblastomas detected by MRI scanning are

asymptomatic. Though the detection of CNS tumors is helpful in determining carrier status, surgery is usually only performed for symptomatic tumors.

### ***Retinal Angiomatosis (See Fig. 11.8)***

This is often the earliest manifestation of VHL disease (Maher et al. 1990a). Retinal angiomatosis are frequently asymptomatic and most occur in the peripheral retina. They have been reported in infancy and in the ninth decade, but the risk of retinal angiomatosis before the age of 5 years is less than 1 % and mean age at diagnosis is 25 years. Early detection of retinal angiomatosis facilitates treatment and prevents blindness. Direct and indirect ophthalmoscopy should be performed on all patients and at-risk relatives (see Table 11.14). Fluorescein angiography can improve the detection of small lesions.



**Fig. 11.8** VHL disease: (a) moderate-sized retinal angioma and (b) fluorescein angiogram of the same lesion (Reproduced with permission from Cambridge University Press)

**Table 11.14** Typical screening protocol for VHL disease in affected patients and at-risk relatives

#### *Affected patient or gene carrier*

Annual physical examination and urine testing

Annual direct and indirect ophthalmoscopy

MRI brain scan every 3 years to 50 years of age and every 5 years thereafter

Annual abdominal MRI scan

Annual 24-h urine collection for catecholamines and VMAs (plasma metanephrines more sensitive)

#### *At-risk relative*

Annual physical examination and urine testing

MRI brain scan every 3 years from 15 to 40 years of age and then every 5 years until 60 years of age

Annual renal MRI or ultrasound scan from 16 to 65 years of age

Annual 24-h urine collection for catecholamine and VMAs (plasma metanephrines more sensitive)

## ***Renal Cell Carcinoma***

In cross-sectional studies, 25–30 % of VHL patients have had clear cell RCC (Maher et al. 1990a). The risk of RCC in VHL disease was initially underestimated because the mean age at RCC diagnosis (44 years) is older than for retinal angioma (25 years) and cerebellar hemangioblastoma (29 years), but since emerging as the leading cause of mortality in VHL disease (Maher et al. 1990a), the importance of presymptomatic renal surveillance has been recognized. The clinical presentation and risk of metastasis in RCC complicating VHL disease are similar to those of sporadic nonfamilial tumors. However, tumors in VHL disease occur at an earlier age and are often multiple and bilateral. Renal cysts may be detected in the second decade, and RCC has been detected as early as age of 16 years. RCC may arise from the wall of renal cysts, and complex cysts require careful follow-up. Renal tumors and cysts may be detected by ultrasonography or computer tomography, but MRI scanning is preferred for routine screening as it is more sensitive than ultrasonography and avoids repeated radiation exposure. The management of renal cancer in VHL disease is motivated by a conservative nephron-sparing approach. Thus it is usual to follow small asymptomatic tumors by serial imaging until they reach about 3 cm diameter. At that stage, conservative renal surgery is performed with the aim of conserving functioning renal tissue for as long as possible. Follow-up of VHL patients treated by nephron-sparing surgery reveals a high incidence of local recurrence from new primary tumors, but a low risk of distant metastasis. In contrast, 25 % of VHL patients with more advanced RCC (>3 cm) develop metastatic disease (Walther et al. 1999a). Repeated partial nephrectomies may eventually compromise renal function, and in such cases dialysis is instigated – though renal transplantation is also an option. It appears that immunosuppression does not affect adversely the underlying course of VHL disease, and the prognosis of VHL patients after transplantation appears similar to that of other comparable groups (Goldfarb et al. 1998).

## ***Pheochromocytoma***

There are clear interfamilial differences in predisposition to pheochromocytoma in VHL disease. In a minority of families, pheochromocytoma is the most frequent complication of this disease but in other families it is rare (Maher et al. 2011). VHL disease has been subclassified according to the presence (type 2) or absence (type 1) of pheochromocytoma. In most cases, pheochromocytoma-positive VHL families also have a high incidence of renal cancer (type 2B), but in some type 2 VHL disease families, pheochromocytoma is common and renal carcinoma is rare (type 2A). In addition rare *VHL* missense mutations may cause a familial pheochromocytoma-only phenotype (type 2C) (Woodward et al. 1997). Up to 11 % of patients with apparently sporadic pheochromocytoma may have a germline *VHL* mutation (Neumann et al. 2002). Both adrenal and extra-adrenal



pheochromocytomas can occur in VHL disease. Pheochromocytoma in VHL disease patients is usually associated with missense mutations (see below), and although the overall risk of malignancy in pheochromocytomas is ~10 %, the rate in VHL disease appears to be lower (~5 %).

## ***Pancreas***

Pancreatic cysts and tumors are relatively common features of VHL disease. Multiple cysts are the most frequent pancreatic manifestation and are present in most older patients. However pancreatic cysts rarely impair pancreatic function. Pancreatic tumors occur in ~10 % of cases. A high frequency of that malignancy has been reported in VHL-associated islet cell tumors, and surgery is indicated in tumors with a diameter of 3 cm or more (Libutti et al. 1998).

## ***Endolymphatic Sac Tumors (ELSTs)***

ELSTs have only been recognized as a specific component of VHL disease relatively recently. In a large survey of VHL patients using MRI and CT scans, Manski et al. (1997) found that 11 % of patients with VHL disease had an ELST. Hearing loss is the most common symptom of ELST, but tinnitus and vertigo also occur in many cases. Hence an ELST should be considered in all VHL patients who complain of hearing loss. However ELSTs are frequently asymptomatic and surgical intervention is not always indicated.

## ***Molecular Genetics***

The VHL disease gene maps to chromosome 3p25 and was isolated in 1993 (Latif et al. 1993). Germline mutations may be detected in ≥95 % of patients, and genotype–phenotype correlations have been described such that large deletions and protein-truncating mutations are associated with a low risk of pheochromocytoma, and specific missense mutations may produce a high risk of pheochromocytoma (type 2 families). Families with a high frequency of pheochromocytoma (types 2A, 2B, and 2C) usually have a surface missense mutation, whereas type 1 families have mostly germline deletions or truncating mutations. Regular screening of patients affected by VHL disease and of at-risk relatives is important to detect tumors at an early stage and to establish the carrier status for at-risk individuals (see Table 11.14). Molecular genetic analysis enables the screening protocols to be modified according to an individual's risk so that screening frequency may be reduced or discontinued as appropriate.

## Werner Syndrome (OMIM #277700)

This is a rare autosomal recessive disorder with a reported prevalence that varies from 1 in  $10^5$  in Japan to 1 in  $10^6$ – $10^7$  outside of Japan. There also appears to be an increased incidence in Sardinia. Werner syndrome (WS) is characterized by features of premature senescence and short stature with loss of subcutaneous fat and muscle, stocky trunk and slender limbs, a thin face with beaked nose, and a high-pitched and hoarse voice. The clinical features of senescence develop from the second decade, with premature greying of the hair from the third decade, generalized hair loss, juvenile cataracts from the third decade, premature arteriosclerosis and calcification of blood vessels with coronary heart disease, osteoporosis, metastatic calcification, and scleropoikiloderma of the skin giving an aged appearance. Diabetes mellitus and hypogonadism may be associated. There may be osteoporosis with ankylosis and destruction of joints and muscle atrophy, and hyperkeratosis over bony prominences and on the soles of the feet, which may ulcerate. There may be areas of hyperpigmentation and hypopigmentation of the skin, with lentigines. The clinical diagnosis is based on the presence of four cardinal signs which are found in more than 95 % of cases. These are cataracts, characteristic skin changes (scleropoikiloderma), short stature, and greying or loss of hair. If all the cardinal signs are present after the age of 10, and two additional signs from the above list (e.g., diabetes, atherosclerosis) are present, then the diagnosis is made clinically. Mutation analysis of *WRN* is used to confirm the clinical diagnosis (Coppede 2012).

About 10 % of affected individuals develop tumors, predominantly of types uncommon in the general population, notably of connective tissue or mesenchymal origin, such as soft tissue sarcomas, osteosarcomas, uterine myosarcomas, meningiomas, and adenomas of the thyroid, parathyroid, adrenal cortex, breast, and liver (Epstein et al. 1966; Goto et al. 1996). Thyroid carcinomas and melanomas have been reported more frequently in Japanese than in Caucasian WS patients. Most WS patients die of atherosclerosis or cancer during the fourth decade of life. Cultured cells from WS patients show chromosome instability and hypersensitivity to DNA cross-linking agents (Moser et al. 2000).

WS is caused by loss-of-function mutations in a gene (*WRN*, *RECQL2*) at chromosome 8p12 that encodes a protein, WRN, which is a member of the RECQ DNA helicase family (Yu et al. 1996; Nishijo et al. 2004). In culture, cells from WS patients show increased chromosomal aberrations, premature senescence, and telomere shortening. Defects in DNA replication are observed. Most mutations result in absence of the WRN protein, although some deleterious missense mutations have been reported (Coppede 2012).

Chen et al. (2003) found that 20 % of patients referred to an international registry for molecular diagnosis of Werner syndrome had wild-type *WRN* mutation analysis. Sequence analysis of the *LMNA* gene (which is mutated in a rare childhood syndrome of premature aging, Hutchinson–Gilford syndrome, and other disorders) in this subset revealed a heterozygous *LMNA* missense mutation in 15 % of cases. This atypical form of WS typically has an earlier onset of aging phenotypes than *RECQL2*-associated classical WS cases but lacks cataracts and diabetes.

Experiments in mice suggest that the short stature seen in WS and related progeroid conditions is a result of suppression of the somatotrophic axis in response to excessive DNA damage – the so-called survival response. It seems likely that genome maintenance, premature aging, and predisposition to cancer are tightly linked (Hoeijmakers 2009).

### **Wiskott–Aldrich syndrome, OMIM #301000; X-Linked Thrombocytopenia, #313900; Intermittent X-Linked Thrombocytopenia, #313900; and X-Linked Neutropenia, #300299**

All the above conditions are caused by mutations in the gene *WASP*; which condition develops depends on the type and/or position of the mutations found in *WASP* (see below). The classic X-linked recessive disorder, Wiskott–Aldrich syndrome (WAS), is rare – its incidence is between 1 and 10 per million persons. It is characterized by immunodeficiency, eczema, and microthrombocytopenia. The typical presentations (often at birth) include mucocutaneous petechiae, bruising, and bloody diarrhea. Severe eczema often develops in infancy or childhood. Hepatosplenomegaly can occur. Complications include susceptibility to pyogenic infection (especially otitis media and pneumonia), arthritis, autoimmune disease, and lymphoma. Death in childhood may occur from overwhelming bacterial or viral infections. Eczema can be complicated by molluscum contagiosum, herpes simplex, and bacterial infections (Thrasher 2009). Patients have small platelets, and the immunodeficiency involves both T cell and B cell function. There is low antigen-induced lymphocyte proliferation, with low IgM and defective antibody production. There is progressive loss of lymphoid elements normally found in the thymus, spleen, lymph nodes, etc. Malignancy of the reticuloendothelial system, lymphomas, and lymphomatoid granulomatosis are common, being the cause of death in about 10 % of cases (ten Benschel et al. 1964). However, by the age of 30 years, the risk of non-Hodgkin lymphoma approaches 100 %. The basic defect underlying all four disorders is dysregulated actin polymerization in hematopoietic cells on account of loss or inappropriate activity of the WAS protein, WASP.

The *WASP* gene was identified in 1994 (Derry et al. 1994a, b). Since then, numerous *WASP* mutations have been characterized, including a small number of hot spot mutations (~25 % of all identified mutations) and genotype–phenotype correlations have also been characterized. *WASP* mutations may result in four distinct phenotypes: the classic WAS triad of thrombocytopenia/small platelets, recurrent infections as a result of immunodeficiency, and eczema; the milder X-linked thrombocytopenia (XLT) variant, where eczema, immune deficiency, infection, and cancer may or may not occur; intermittent XLT, where microthrombocytopenia may be the sole manifestation; and X-linked neutropenia (XLN) where congenital neutropenia and associated infections are the only manifestations. Persons with a normal-sized but mutated protein (usually reduced in quantity), associated with a

missense mutation in exons 1–3 (or in-frame deletions elsewhere in *WASP*), nearly always have XLT. Missense mutations that disrupt autoinhibition cause XLN, whereas other missense mutations can cause IXLN (Thrasher 2009). Those with mutations leading to complete loss of protein expression or expression of a truncated protein have a more severe classical WAS phenotype and a higher risk of malignancy (Imai et al. 2004; Jin et al. 2004). Treatment of severely affected children is with intravenous immunoglobulins (even if total IgG levels are normal) and prompts hematopoietic stem cell transplantation.

### **X-Linked Lymphoproliferative Disorder (Duncan Disease) (OMIM 308240)**

This condition affects about 3 per million males, and the gene has been mapped to Xq25. Affected males are susceptible to severe infectious mononucleosis infections (fatal in 50 %, often in childhood), and 25 % develop malignant lymphoma, typically Burkitt-type non-Hodgkin lymphoma in the ileocecal region, but CNS, hepatic, and renal lymphomas are also common. Systemic vasculitis is a rare complication (Dutz et al. 2001). X-linked lymphoproliferative disorder is caused by mutations in the SH2 domain protein 1A (*SH2D1A*) gene (Sumegi et al. 2000). At least one-quarter of all mutations are missed by direct sequencing, so there may be a role for other, function-based assays in definite cases or in possible heterozygotes (Tabata et al. 2005).

### **Xeroderma Pigmentosum (OMIM #278700, 610651, 278720, 278730, 278740, 278760, 278780, and variant 278750)**

This is a heterogeneous group of autosomal recessive disorders with a prevalence of about 1 in 70,000 of the population. It is characterized by hypersensitivity to UV light and a high incidence of UV-induced skin cancers. Clinical onset is before the age of 18 months in 50 %. Freckle-like skin lesions with erythema develop in sun-exposed skin in the first few years of life, and there may be extreme sunlight sensitivity (see Fig. 11.6). Macules of increased pigmentation develop on the skin and mucous membranes, and achromic areas may also occur. Subsequently, there is an atrophic and telangiectatic stage in which the skin becomes dry and scaly, with atrophy and spotted dyschromia. Hyperkeratotic plaques, keratomas, keratoacanthomas, fibromas, angiomyomas, cutaneous horns, and other benign tumors ensue, and there may be facial ulcerations. Multiple malignant basal and squamous cell carcinomas and malignant melanoma develop in sun-exposed areas; the risk for malignancy is up to 2,000-fold increase above normal. The median age at onset for skin cancer in XP has been estimated to be 8 years, compared with 60 years in the general population. Squamous cell carcinomas, sarcomas, melanomas, and epitheliomas may develop in the eyes and mucous membranes, and squamous cell carcinomas of the

tongue and oropharynx may occur, with a relative risk of 10,000 times normal. Other malignant tumors may develop, including neurinomas, sarcomas, and adenocarcinomas. It has been suggested that there is also a 10–20-fold increased incidence of internal neoplasms, such as lung, uterine, brain, breast, or testicular tumors in XP. Actinic damage to the eyes may cause keratitis and conjunctivitis, which can lead to symblepharon and neoplasia, particularly at the corneoscleral junction. Entropion and ectropion may occur. Death results from disseminated tumors, usually by the second or third decade (Giannelli and Pawsey 1976; Kraemer and Slor 1985).

De Sanctis–Cacchione syndrome emphasized neurological involvement in a subgroup of XP patients. Neurological complications are variable and include progressive mental deficiency, microcephaly, ataxia, choreoathetosis, spasticity, sensorineural deafness, and lower motor neuron and cranial nerve damage. Onset of these neurological abnormalities may be in infancy or later in childhood and may be mild or severe. They develop in about 18 % of cases of XP (Kraemer and Slor 1985). They can occur in any subgroup of XP but do so most commonly in complementation group D (XPD) (see below). Loss or absence of neurons may be demonstrated in the cerebrum or cerebellum at autopsy in these cases. The karyotype is normal, but there is hypersensitivity to chromosomal damage after exposure to UV light.

Different subgroups (complementation groups) of XP are described, each with a different type of mutation reducing the capacity for excision repair of UV-induced DNA damage (Giannelli 1986). These subgroups are associated with different clinical severity. Complementation group A (XPA) includes cases of all degrees of clinical severity, with and without neurological complications; group C (XPC) is the most commonly described; and most are neurologically normal. Cockayne syndrome with XP has been described in single cases (Neilan et al. 2008). The molecular bases for these conditions have been delineated and are due to various defects in solar-induced DNA damage. These defects comprise lack of a functional helicase, endonuclease, or lesion-recognizing protein involved in the initial steps of nucleotide excision repair. Different enzyme defects are found in the different complementation groups. They include proteins involved in recognition of photoproducts (XPE), and of other DNA defects such as pyrimidine dimers (XPA), DNA helicases (XPB, XPD), and endonucleases that perform two incisions (XPG), and single-strand-binding proteins (XPC) (Boulikas 1996; Chu and Mayne 1996). Prenatal diagnosis by chorionic villus sampling is becoming available in those families in which the mutation can be defined at the DNA level.

Mutations in eight genes may cause XP. The genes for group A and group C xeroderma pigmentosum (XPA and XPC) are involved solely in nucleotide excision repair, whereas the XPB and XPD proteins are both components of transcription factor TFIIH, which is involved in nucleotide excision repair, in basal transcription and in activated transcription (Lehmann 2003). All bona fide patients with XPE have a mutation in the *DDB2* gene that encodes the smaller subunit of the heterodimeric damaged DNA-binding protein. XP group F (XPF) is caused by mutations in the *ERCC4* gene and group G (XPG) by mutations in *ERCC5*.

XP variant (XP-V) is indistinguishable from XP clinically, except the neurological features do not develop. Unlike other XP cells belonging to XPA to XPG,

XP-V cells have normal nucleotide excision repair processes, but have defective replication of UV-damaged DNA. This form of XP is caused by mutations in the DNA polymerase eta gene (*POLH*) (Masutani et al. 1999). Suggestions of an increased risk of lung cancer in heterozygote carriers (for all relatives: relative risk, 1.93) (Swift and Chase 1979) have prompted association studies of XP gene variants and lung cancer risk with mixed results (Marin et al. 2004; Benhamou and Sarasin 2005).

Treatment is by protection from sunlight and careful surveillance, with early excision of tumors. Avoidance of UV light should be instigated in childhood, when the apparent health of young children makes this difficult. The use of an UV light meter can be helpful. It is interesting that spontaneous regression of malignant melanoma has been described to occur in XP, although the mechanism for this is not understood (Lynch et al. 1978). Information for patients and their families is available from the xeroderma pigmentosum society (<http://www.xps.org>).

Prenatal diagnosis of XP has been accomplished by demonstrating abnormal levels of DNA repair capacity on measurement of unscheduled DNA synthesis in UV-irradiated fetal amniocytes (Aras et al. 1985) or by mutation analysis.

A separate disorder of increased UVA sensitivity has been described, in which there is an autosomal dominant predisposition to the development of cutaneous pigmented keratoses in sun-exposed skin associated with the development of carcinoma of the uterus and other internal malignancies (clinically more apparent in females) (Atherton et al. 1989). Fibroblasts from affected individuals demonstrated an increased frequency of single-strand breaks in DNA following exposure to long-wave UVA.

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# Appendix

## Genetic Differential Diagnoses by Organ System Neoplasms

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
Adrenal	Adrenocortical neoplasia	Li–Fraumeni syndrome (Latronico et al. 2001; Sameshima et al. 1992; Wagner et al. 1994; Varley et al. 1999; Hisada et al. 1998)	<i>TP53</i>
		Beckwith–Wiedemann syndrome	<i>CDKN1C</i> ( <i>p57KIP2</i> ), <i>NSD1</i>
		Carney complex (Stratakis et al. 2001; Watson et al. 2000; Ohara et al. 1993; Handley et al. 1992; Wallace et al. 1991; Cheung and Thompson 1989; Carney et al. 1985; Kirschner et al. 2000a)	<i>PRKARIA</i>
		Multiple endocrine neoplasia type 1	<i>MEN1</i>
	Adrenocortical hyperplasia	McCune–Albright syndrome	<i>GNAS1</i> (not germline)
		Site-specific adrenocortical hyperplasia	<i>PDE11A</i>
	Adrenocortical carcinoma	Li–Fraumeni syndrome	<i>TP53</i>
	Medulla–pheochromocytoma	von Hippel–Lindau disease (Neumann et al. 2002; Richard et al. 1994; Chen et al. 1995; Crossey et al. 1995; Gross et al. 1996; Glavac et al. 1996; Garcia et al. 1997; Atuk et al. 1998; Friedrich 2001; Eng et al. 1996)	<i>VHL</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Pheochromocytoma–paranglioma syndrome (Neumann et al. 2002; Astuti et al. 2001; Gimm et al. 2000)	<i>SDHA</i> , <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> , <i>SDHAF2</i> , <i>TMEM127</i> , <i>MAX</i>
		Multiple endocrine neoplasia (MEN) type 2 (Langer et al. 2002; Dotzenrath et al. 2001; Skogseid et al. 1995; Beckers et al. 1992)	<i>RET</i>
		Neurofibromatosis type 1 (Lima and Smith 1971; Takayama et al. 2001; Walther et al. 1999; Zoller et al. 1997; Sakaguchi et al. 1996; Ogawa et al. 1994; Chetty and Duhig 1993; Xu et al. 1992; Samuelsson and Samuelsson 1989; Kalff et al. 1982; Samuelsson and Axelsson 1981; Knight et al. 1973; Anneroth and Heimdahl 1978)	<i>NFI</i>
Bladder		Werner syndrome (Monnat 2002)	<i>WRN</i>
		Costello syndrome	<i>HRAS</i>
Brain	Glioma/ glioblastoma	Li–Fraumeni syndrome (Sameshima et al. 1992; Wagner et al. 1994; Varley et al. 1999; Hisada et al. 1998; Birch et al. 1994; Kleihues et al. 1997; Kyritsis et al. 1994; Li et al. 1995; Nichols et al. 2001; Vital et al. 1998; Zhou et al. 1999)	<i>TP53</i>
		Turcot syndrome (HNPCC) (Tamiya et al. 2000; Chan et al. 1999; Taylor et al. 1999; Leung et al. 1998; Van Meir 1998; Buerstedde et al. 1995; Hamilton et al. 1995)	<i>MLH1</i> , <i>MSH2</i> , <i>PMS1</i> , <i>PMS2</i>
		Hereditary retinoblastoma (Elias et al. 2001; Louis and von Deimling 1995; Taylor et al. 2000a)	<i>RBI</i>
	Optic glioma	Neurofibromatosis type 1 (Cnossen et al. 1997, 1998; Bilaniuk et al. 1997; McGaughan et al. 1999; Listerick et al. 1999; Faravelli et al. 1999; North 1998; Shah et al. 2000; Kornreich et al. 2001; Singhal et al. 2002)	<i>NFI</i>
	Trilateral retinoblastoma	Hereditary retinoblastoma (Elias et al. 2001; Louis and von Deimling 1995; Taylor et al. 2000a; Amoaku et al. 1996; Bader et al. 1980; Blach et al. 1994; De Potter et al. 1994; Holladay et al. 1991; Moll et al. 1997; Pesin and Shields 1989)	<i>RBI</i>

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Astrocytoma	Neurofibromatosis type 1 (Bilaniuk et al. 1997; Kubo et al. 1996; Ito et al. 1997; Vinchon et al. 2000; Li et al. 2001; Perry et al. 2001; Gutmann et al. 2002)	<i>NF1</i>
		Tuberous sclerosis complex (O'Callaghan et al. 2000; Nabbout et al. 1999; Nishio et al. 2001; Torres et al. 1998; Turgut et al. 1996; Roszkowski et al. 1995)	<i>TSC1, TSC2</i>
		Melanoma-astrocytoma syndrome (Randerson-Moor et al. 2001; Bahuaui et al. 1998; Greene 1999)	<i>CDKN2A/p16, p14ARF</i>
	Medulloblastoma/ NET	Turcot syndrome (FAP) (Van Meir 1998; Hamilton et al. 1995; Cohen 1982; Jarvis et al. 1988; Todd et al. 1981; Mastronardi et al. 1991)	<i>APC</i>
		Nevoid basal cell carcinoma syndrome (Neblett et al. 1971; Naguib et al. 1982; Lacombe et al. 1990; Kimonis et al. 1997; Taylor et al. 2002; Wolter et al. 1997; Minami et al. 2001)	<i>PTC</i>
		Rhabdoid predisposition syndrome (Sevenet et al. 1999)	<i>SNF5/INI1</i>
	Neurofibromas	Neurofibromatosis type 1 (Zoller et al. 1997; Carey et al. 1979; Riccardi et al. 1979; Sorensen et al. 1986; Szudek et al. 2000; North 2000; Rasmussen and Friedman 2000)	<i>NF1</i>
	Vestibular schwannomas	Neurofibromatosis type 2 (Parry et al. 1996; Kluwe et al. 1996; Welling 1998; Evans et al. 1998, 2000; Evans 1999; Baser et al. 2002)	<i>NF2</i>
	Meningioma	Neurofibromatosis type 2 (Evans 1999; Stemmer-Rachamimov et al. 1997; Antinheimo et al. 1997, 2000; Turgut et al. 1997; Caldemeyer and Mirowski 2001)	<i>NF2</i>
		Neurofibromatosis type 1 (Evans 1999)	<i>NF1</i>
		Cowden syndrome (Eng 2000; Starink et al. 1986; Lyons et al. 1993; Lindboe et al. 1995; Murata et al. 1999)	<i>PTEN</i>
		Werner syndrome (Monnat 2002)	<i>WRN</i>
	Ependymoma	Neurofibromatosis type 2 (Wertelecki et al. 1988)	<i>NF2</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Hemangioma, hemangioblastoma	von Hippel–Lindau syndrome (Couch et al. 2000; Webster et al. 1998)	<i>VHL</i>
	Rhabdoid tumor/atypical teratoid tumor	Rhabdoid predisposition syndrome (Sevenet et al. 1999; Taylor et al. 2000b)	<i>SNF5/INI1</i>
	Cerebellum, dysplastic gangliocytoma (Lhermitte–Duclos disease)	Cowden syndrome (Eng 2000; Starink et al. 1986; Lindboe et al. 1995; Murata et al. 1999; Nowak and Trost 2002; Nowak et al. 2001; Chapman et al. 1998; Thomas and Lewis 1995; Padberg et al. 1991; Robinson and Cohen 2000)	<i>PTEN, SDHB, SDH; KLLN</i> (epimutation)
	Choroid plexus tumors	Li–Fraumeni syndrome (Garber et al. 1990)	<i>TP53</i>
Breast, female	Carcinoma	Hereditary breast–ovarian cancer syndrome (HBOC) (Gayther et al. 1995, 1997; Couch et al. 1996; Neuhausen et al. 1996; Lancaster et al. 1996; Caligo et al. 1996; Agnarsson et al. 1998; Ligtenberg et al. 1999)	<i>BRCA1, BRCA2</i>
		Cowden syndrome/BRRS (Eng 2000; Starink et al. 1986; Schrager et al. 1998; Tsubosa et al. 1998; Marsh et al. 1998, 1999)	<i>PTEN, SDHB, SDH; KLLN</i> (epimutation)
		Li–Fraumeni syndrome (Hisada et al. 1998; Birch et al. 1994, 1998, 2001; Nichols et al. 2001; Bang et al. 1995; Varley et al. 1995; Huusko et al. 1999; Hung et al. 1999)	<i>TP53</i>
		Peutz–Jeghers syndrome (Boardman et al. 1998; Burdick and Prior 1982)	<i>LKB1/STK11</i>
		Ataxia–telangiectasia heterozygotes (Lavin 1998; Janin et al. 1999; Larson et al. 1997; Broeks et al. 2000; Sommer et al. 2002)	<i>ATM</i>
		Werner syndrome (Monnat 2002)	<i>WRN</i>
Breast, male	Carcinoma	HBOC (Schubert et al. 1997; Hakansson et al. 1997; Wolpert et al. 2000; Lobaccaro et al. 1993)	<i>BRCA2 (BRCA1)</i>
		Cowden syndrome (Eng 2000; Starink et al. 1986; Fackenthal et al. 2001)	<i>PTEN</i>
		Reifenstein syndrome (Wooster et al. 1992)	<i>AR</i>

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Klinefelter syndrome (van Geel et al. 1985; Hultborn et al. 1997)	XXY
Colorectum	Adenocarcinoma	Hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch et al. 1985a; Lynch and Lynch 1995; Leach et al. 1993; Papadopoulos et al. 1994; Aaltonen and Peltomaki 1994; Froggatt et al. 1995; Akiyama et al. 1997; Berends et al. 2002)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		Familial adenomatous polyposis (FAP) syndrome (Moisio et al. 2002; Presciuttini et al. 1994; Fodde and Khan 1995; Bunyan et al. 1995; Friedl et al. 1996; Armstrong et al. 1997; Eccles et al. 1997; Soravia et al. 1998; Heinimann et al. 1998)	<i>APC</i>
		Juvenile polyposis syndrome <i>SMAD4</i> (Zhou et al. 2001; Woodford-Richens et al. 2000, 2001; Howe et al. 2002)	<i>MADH4, BMPRIA</i>
		<i>BMPRIA</i> (Zhou et al. 2001; Friedl et al. 2002; Howe et al. 2001)	
		Peutz–Jeghers syndrome (Boardman et al. 1998; Burdick and Prior 1982; Giardiello et al. 1987; Linos et al. 1981)	<i>LKB1/STK11</i>
		Hereditary mixed polyposis syndrome(s) (Whitelaw et al. 1997; Thomas et al. 1996)	
		Autosomal recessive polyposis–colon cancer syndrome	<i>MYH</i>
		Birt–Hogg–Dubé syndrome	<i>BHD</i>
		Cowden syndrome	<i>PTEN</i>
	Polyp – adenoma	HNPCC (Watanabe et al. 1996; Watne 1997; Souza 2001; Cao et al. 2002)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		FAP (Soravia et al. 1998; Wu et al. 1998; Brensinger et al. 1998; Wallis et al. 1999; Gebert et al. 1999; Giarola et al. 1999)	<i>APC</i>
		Hereditary mixed polyposis syndrome(s) (Whitelaw et al. 1997)	<i>PTEN, Others</i>
		Autosomal recessive polyposis–colon cancer syndrome (MYH-associated polyposis syndrome)	<i>MYH</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Polyp – hamartoma	Juvenile polyposis syndrome (Zhou et al. 2001; Friedl et al. 2002; Entius et al. 1999; Sachatello and Griffen 1975; Howe et al. 1998a; Houlston et al. 1998) Peutz–Jeghers syndrome (Hanna et al. 1994) Cowden syndrome/BRRS (Eng 2000; Starink et al. 1986; Marsh et al. 1998; Hanna et al. 1994; Hizawa et al. 1994) Hereditary mixed polyposis syndrome(s) (Whitelaw et al. 1997; Thomas et al. 1996) Tuberous sclerosis complex (Devroede et al. 1988) Gorlin syndrome Birt–Hogg–Dubé syndrome	<i>MADH4</i> , <i>BMPRIA</i> <i>LKB1/STK11</i> <i>PTEN</i> <i>TSC1</i> , <i>TSC2</i> <i>PTCH1</i> <i>BHD</i>
Esophagus	Adenocarcinoma	Familial barrett esophagus–adenocarcinoma (Romero et al. 1997)	<i>MSR1</i>
	Squamous cell carcinoma	Familial esophageal squamous cell cancer (Hemminki and Jiang 2002) Fanconi anemia (Linares et al. 1991; Gendal et al. 1988; Kozarek and Sanowski 1981) Tylosis and esophageal cancer (TOC) (Risk et al. 1999; Marger and Marger 1993; Ellis et al. 1994; Stevens et al. 1996; Maillefer and Greydanus 1999)	<i>FANC-X</i>
Eye	Retinoblastoma, retinoma	Hereditary retinoblastoma (Cavenee et al. 1985; Goddard et al. 1990; Kratzke et al. 1994; Cowell and Cragg 1996; Harbour 1998; Lohmann 1999; Alonso et al. 2001)	<i>RB1</i>
	Angioma, hemangioblastoma	von Hippel–Lindau syndrome (Glavac et al. 1996; Webster et al. 1998; Hes et al. 2000; Zbar et al. 1999)	<i>VHL</i>
	Melanoma	Li–Fraumeni syndrome (Hisada et al. 1998; Jay and McCartney 1993) Ocular melanocytosis (Singh et al. 1996, 1998) Familial atypical mole melanoma (FAMMM)/P16 (Singh et al. 1995) HBOC (Iscovich et al. 2002)	<i>TP53</i> <i>P16</i> <i>BRCA2</i>



**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Squamous cell carcinoma, anterior eye Hamartoma	Site-specific/early onset, with or without cutaneous melanoma	<i>BAP1</i>
		Xeroderma pigmentosum (Goyal et al. 1994; Hertle et al. 1991; Sarma et al. 1973)	<i>XP-x</i>
		Tuberous sclerosis complex (Gelissen et al. 1990; Kiribuchi et al. 1986)	<i>TSC1, TSC2</i>
		FAP (CHRPE)	<i>APC</i>
Head and neck	Squamous cell carcinomas	Fanconi anemia (Oksuzoglu and Yalcin 2002; Somers et al. 1995; Lustig et al. 1995; Kaplan et al. 1985)	<i>FANC-X</i>
		Bloom syndrome (Berkower and Biller 1988)	<i>BLM</i>
		Dyskeratosis syndrome (Drachtman and Alter 1995)	<i>TERC</i> (AD), <i>DKC1</i> (X-linked)
		Xeroderma pigmentosum (Kraemer et al. 1987; Patton and Valdez 1991; Shen et al. 2001)	<i>XP-x</i>
	Melanoma: nasal mucosa	Werner syndrome (Monnat 2002; Goto et al. 1996)	<i>WRN</i>
	Sebaceous carcinoma	Muir-Torre syndrome (40% eyelid) (Lynch et al. 1985b; Burgdorf et al. 1986; Cohen et al. 1995; Serleth and Kissen 1998; Coldron and Reid 2001)	<i>MSH2, MLH1</i>
Heart	Myxoma	Carney complex (Carney et al. 1985, 1986; Stratakis et al. 1996; Kirschner et al. 2000b; Edwards et al. 2002)	<i>PRKARIA</i>
	Rhabdomyoma	Tuberous sclerosis complex (Nir et al. 1995; See et al. 1999; Jozwiak et al. 1994; Webb and Osborne 1992; Watson 1991)	<i>TSC1, TSC2</i>
Hematological	Leukemia, acute	Li-Fraumeni syndrome (Hisada et al. 1998; Birch et al. 1994; Kleihues et al. 1997; Imamura et al. 1994)	<i>TP53</i>
		Bloom syndrome (Passarge 1991; Gretzula et al. 1987; German et al. 1977; Poppe et al. 2001)	<i>BLM</i>
	Leukemia, acute myeloid	Fanconi anemia (Auerbach and Allen 1991; Faivre et al. 2000)	<i>FANC-x</i>
		Emberger syndrome <sup>a</sup> Familial thrombocytopenia and predisposition to AML (Downton et al. 1985; Arepally et al. 1998; Song et al. 1999; Michaud et al. 2002)	<i>GATA2</i> <i>RUNX1/AML1</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Amegakaryocytic thrombocytopenia (Tonelli et al. 2000; Germeshausen et al. 2001)	<i>C-MPL</i>
		Diamond-Blackfan anemia (Janov et al. 1996; Krijanovski and Sieff 1997; Freedman 2000)	<i>RPS19</i>
		Shwachman–Diamond syndrome (Cipolli 2001; Smith et al. 1996; Woods et al. 1981)	<i>SBDS</i>
		Severe congenital neutropenia/Kostmann syndrome (Li and Horwitz 2001; Welte and Dale 1996)	<i>ELA2, GFI1</i>
		Werner syndrome (Monnat 2002; Tao et al. 1971)	<i>WRN</i>
Leukemia, acute lymphoid, PLL		Ataxia telangiectasia (Peterson et al. 1992; Taylor et al. 1996; Boultonwood 2001)	<i>ATM</i>
		Nijmegen breakage syndrome (Varon et al. 2001)	<i>NBS1</i>
Leukemia, juvenile chronic myeloid		Neurofibromatosis type 1 (Clark and Hutter 1982; Zvulunov et al. 1995; Hasle et al. 1995; Jang et al. 1999)	<i>NFI</i>
Lymphoma, non-Hodgkin		Ataxia telangiectasia (Taylor et al. 1996; Stankovic et al. 1998; Murphy et al. 1999; Seidemann et al. 2000)	<i>ATM</i>
		Nijmegen breakage syndrome (Weemaes et al. 1994; Seidemann et al. 1999)	<i>NBS1</i>
		Bloom syndrome (Passarge 1991; Gretzula et al. 1987; Kaneko et al. 1997)	<i>BLM</i>
		Autoimmune lymphoproliferative syndrome/Canale–Smith syndrome (Peters et al. 1999; Straus et al. 1997, 2001; Vaishnav et al. 1999; Jackson and Puck 1999; Rieux-Laucat et al. 1999; Drappa et al. 1996)	<i>FAS, FASL, CASP10</i>
		Chediak–Higashi syndrome (Argyle et al. 1982; Dent et al. 1966)	<i>LYST</i>
		Wiskott–Aldrich syndrome (Cotelingam et al. 1985)	<i>WAS</i>
		Duncan disease (X-linked lymphoproliferative disease) (Purtulo et al. 1977, 1982; Hamilton et al. 1980; Purtulo 1981)	<i>SH2D1A</i>

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Hodgkin disease	Autoimmune lymphoproliferative syndrome/Canale–Smith syndrome (Peters et al. 1999; Straus et al. 1997, 2001; Rieux-Laucat et al. 1999; Drappa et al. 1996)	<i>FAS, FASL, CASP10</i>
		Ataxia telangiectasia (Boultonwood 2001; Murphy et al. 1999; Seidemann et al. 2000; Harris and Seeler 1973; Frizzera et al. 1980; Hecht and Hecht 1990; Weyl Ben Arush et al. 1995; Olsen et al. 2001)	<i>ATM</i>
		Wiskott–Aldrich syndrome (Cotelingam et al. 1985; Frizzera et al. 1980)	<i>WAS</i>
		Nijmegen breakage syndrome (Seidemann et al. 2000)	<i>NBS</i>
		Emberger syndrome	<i>GATA2</i>
Intestine, small	Carcinoma (ampullary)	FAP (Ohsato et al. 1977; Norton and Gostout 1998; Sellner 1990)	<i>APC</i>
	Carcinoma (any location)	HNPCC (Watson and Lynch 1993; Bisgaard et al. 2002)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		Peutz–Jeghers syndrome (Seidemann et al. 2000; Sellner 1990; Buckley et al. 1997; Luk 1995)	<i>LKB1/STK11</i>
		Juvenile polyposis syndrome (Luk 1995)	<i>MADH4, BMPRIA</i>
	Stromal tumor (GIST)	Hereditary gastrointestinal stromal tumor (Hirota et al. 2002; Handra-Luca et al. 2001; Maeyama et al. 2001; Isozaki et al. 2000; Nishida et al. 1998)	<i>KIT, PDGFA; SDHB/D</i> (in Carney Dyad)
	Carcinoid tumor	Neurofibromatosis type 1 (Chen et al. 1993; Benharroch et al. 1992; Stamm et al. 1986)	<i>NF1</i>
		MEN 1 (Carty et al. 1998; Bordi et al. 1997)	<i>MEN1</i>
Kidney	Renal cell carcinoma, clear cell	von Hippel–Lindau syndrome (Friedrich 2001; Maher et al. 1990, 1995, 1996; Walker 1998; Richards et al. 1998)	<i>VHL</i>
		Birt–Hogg–Dubé syndrome (Nickerson et al. 2002; Zbar et al. 2002; Toro et al. 1999)	<i>BHD</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Cowden syndrome (Eng 2000; Starink et al. 1986; Haibach et al. 1992)	<i>PTEN, SDHB, SDHD; KLLN</i> (epimutation)
		Hereditary clear cell renal carcinoma (Woodward et al. 2000; Bodmer et al. 2002; Podolski et al. 2001; Druck et al. 2001; Eleveld et al. 2001; Kanayama et al. 2001)	
		Werner syndrome (Monnat 2002)	<i>WRN</i>
	Renal cell carcinoma, papillary	Familial papillary renal cell cancer (Malchoff et al. 2000; Olivero et al. 1999; Schmidt et al. 1997)	<i>MET</i>
		Multiple leiomyomatosis syndrome (Kiuru et al. 2001; Tomlinson et al. 2002)	<i>FH</i>
		Tuberous sclerosis complex (Sampson 1996; Al-Saleem et al. 1998)	<i>TSC1, TSC2</i>
		Hyperparathyroidism–jaw tumor syndrome (Haven et al. 2000)	<i>HRPT2</i>
		Birt–Hogg–Dube syndrome (Nickerson et al. 2002; Zbar et al. 2002; Toro et al. 1999; Khoo et al. 2001)	<i>BHD</i>
		Cowden syndrome	<i>PTEN, SDHB, SDHD; KLLN</i> (epimutation)
	Renal pelvis, transitional cell	HNPCC (Muir–Torre syndrome) (Lynch and Lynch 1994, 1995; Honchel et al. 1994)	<i>MSH2, MLH1</i>
	Angiomyolipoma	Tuberous sclerosis complex (Sampson 1996; Schillinger and Montagnac 1996; O’Hagan et al. 1996)	<i>TSC1, TSC2</i>
	Oncocytoma	Tuberous sclerosis complex (O’Hagan et al. 1996; Green 1987; Ruckle et al. 1993)	<i>TSC1, TSC2</i>
		Birt–Hogg–Dube (Nickerson et al. 2002)	<i>BHD</i>
		Cowden syndrome	<i>PTEN, SDHB, SDHD; KLLN</i> (epimutation)
	Wilms tumor	Hereditary Wilms tumor syndrome (Kaplinsky et al. 1996; Pelletier et al. 1991a; Little and Wells 1997; Dome and Coppes 2002)	<i>WT1</i>
		WAGR (Koufos et al. 1989; Grundy et al. 1995)	<i>WT1</i> , contiguous gene deletions
		Beckwith–Wiedemann syndrome (Koufos et al. 1989; Grundy et al. 1995; Cohen and Kurzrock 1995)	<i>CDKN1C</i> ( <i>p57KIP2</i> ), <i>NSD1</i>

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Hyperparathyroidism–jaw tumor syndrome (Haven et al. 2000; Cavaco et al. 2001; Hobbs et al. 1999; Szabo et al. 1995)	<i>HRPT2</i>
		Denys–Drash syndrome (Little and Wells 1997; Pelletier et al. 1991b; Schumacher et al. 1998; Heathcott et al. 2002)	<i>WT1</i>
	Rhabdoid tumor/atypical teratoid tumor	Rhabdoid predisposition syndrome (Sevenet et al. 1999)	<i>SNF5/INI1</i>
	Neuroblastoma	Site-specific neuroblastoma Costello syndrome	<i>ALK, PHOX2B</i> <i>HRAS</i>
Liver	Hepatoblastoma	FAP (Garber et al. 1988; Hughes and Michels 1992; Giardiello et al. 1996; Gruner et al. 1998; Lynch et al. 2001)	<i>APC</i>
		Beckwith–Wiedemann syndrome (DeBaun and Tucker 1998)	<i>CDKN1C</i> ( <i>p57KIP2</i> ), <i>NSD1</i>
	Adenoma/carcinoma	Werner syndrome (Monnat 2002)	<i>WRN</i>
		Fanconi anemia (Alter 1996)	<i>FANC-x</i>
		Beckwith–Wiedemann syndrome (DeBaun and Tucker 1998)	<i>CDKN1C</i> ( <i>p57KIP2</i> ), <i>NSD1</i>
Ovary	Carcinoma	HBOC (Meindl 2002; Sarantaus et al. 2001; Schoumacher et al. 2001; Pharoah et al. 1999)	<i>BRCA1, BRCA2</i>
		HNPCC (Brown et al. 2001; Watson et al. 2001; Cohn et al. 2000; Aarnio et al. 1999)	<i>MLH1, MSH2,</i> <i>MSH6, PMS1,</i> <i>PMS2</i>
	Germ cell	Dysgenetic gonads (XY karyotype) (Liu et al. 1995; Soh et al. 1992; Muller et al. 1992; Damjanov and Klauber 1980; Cussen and MacMahon 1979; Schellhas 1974; Teter 1970)	<i>DHH</i>
	Granulosa cell	Peutz–Jeghers syndrome (Rodu and Martinez 1984; Young et al. 1984; Clement et al. 1979; Christian 1971)	<i>LKB1/STK11</i>
		Ollier disease (Young et al. 1984; Asirvatham et al. 1991; Velasco-Oses et al. 1988)	<i>PTHR1</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
Pancreas	Sertoli-Leydig cell	Maffucci syndrome (Young et al. 1984; Tanaka et al. 1992)	<i>PTHR1</i>
		DICER1 syndrome	<i>DICER1</i>
	Carcinoma	HNPCC (Yamamoto et al. 2001; Wei et al. 2002; Park et al. 1999)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		Familial site-specific pancreatic cancer (Gates and Holladay 2002)	<i>BRCA2</i>
		Hereditary pancreatitis (Hengstler et al. 2000; O'Reilly and Kingsnorth 2000; Lowenfels et al. 1997)	<i>CFTR, SPINK, TRYP</i>
		HBOC (Murphy et al. 2002; Berman et al. 1996)	<i>BRCA2</i>
		Hereditary melanoma/FAMMM (Lynch et al. 2002; Vasen et al. 2000; Gruis et al. 1995; Lynch and Fusaro 1991)	<i>CDKN2A(p16)</i>
		von Hippel–Lindau syndrome (Libutti et al. 2000, 1998; Hammel et al. 2000)	<i>VHL</i>
		Peutz–Jeghers syndrome (Hemminki 1999)	<i>LKB1/STK11</i>
		MEN 1 (Broughan et al. 1986; Dean et al. 2000; Lowney et al. 1998)	<i>MEN1</i>
		von Hippel–Lindau syndrome (Curley et al. 1998; Hough et al. 1994; Binkovitz et al. 1990)	<i>VHL</i>
		Neurofibromatosis type 1	<i>NF1</i>
	Islet cell neoplasias		
Paraganglia	Paraganglioma	Hereditary pheochromocytoma–paraganglioma syndrome (Dannenberg et al. 2002; Cascon et al. 2002; Baysal et al. 2002)	<i>SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX</i>
		von Hippel–Lindau syndrome (Reichardt et al. 2002; Baghai et al. 2002; Chew 2001)	<i>VHL</i>
		MEN 2 (Chew 2001)	<i>RET</i>
		Neurofibromatosis type 1 (Chew 2001)	<i>NF1</i>
		MEN 1	<i>MEN1</i>
Parathyroid	Adenoma/hyperplasia	MEN 1 (Duh et al. 1987; Oberg et al. 1989; Sato et al. 2000)	<i>MEN1</i>
		MEN 2 (Eng et al. 1996; Duh et al. 1987; Howe et al. 1993; Kraimps et al. 1996)	<i>RET</i>
		Familial benign hypercalcemia (mild hyperparathyroidism)	<i>CASR</i>

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Carcinoma	Hyperparathyroidism–jaw tumor syndrome (Haven et al. 2000; Cavaco et al. 2001)	<i>CDC73 (HRPT2)</i>
		Familial isolated hyperparathyroidism (FIHP)	<i>CDC73 (HRPT2)</i>
		Hyperparathyroidism–jaw tumor syndrome	<i>CDC73 (HRPT2)</i>
Pituitary	Adenoma	MEN 1 (Carty et al. 1998; Oberg et al. 1989; Samaan et al. 1989; Wilkinson et al. 1993; Calender et al. 1995; Cebrian et al. 1999; Verges et al. 2002)	<i>MEN1</i>
		Carney complex (Carney et al. 1985; Kirschner et al. 2000a; Stratakis et al. 1996; Carney and Stratakis 1998; Stratakis 2001)	<i>PRKRIA</i>
		Site-specific pituitary adenoma	<i>AIP</i>
Prostate	Carcinoma	Hereditary prostate cancer syndromes (Wang et al. 2002; Simard et al. 2002)	
		HBOC (Gronberg et al. 2001; Sigurdsson et al. 1997; Tulinius et al. 2002)	<i>BRCA1, BRCA2</i>
Sarcoma	Osteosarcoma, soft tissue sarcoma	Li–Fraumeni syndrome (Hisada et al. 1998; Toguchida et al. 1992; Soussi et al. 1993)	<i>TP53</i>
		Werner syndrome (Goto et al. 1996; Bjornberg 1976)	<i>WRN</i>
		Hereditary retinoblastoma (Smith and Donaldson 1991; Wong et al. 1997)	<i>RBI</i>
		Neurofibromatosis type 1 (Zoller et al. 1997; Samuelsson and Axelsson 1981; Hayani et al. 1992)	<i>NFI</i>
		Rothmund–Thomson syndrome (Cumin et al. 1996; Lindor et al. 2000; Spurney et al. 1998; Wang et al. 2001)	<i>RECQL4</i>
		Werner syndrome (Monnat 2002)	<i>WRN</i>
	Soft tissue sarcoma (mainly rhabdomyosarcoma)	Costello syndrome	<i>HRAS</i>

(continued)



**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Malignant peripheral nerve sheath tumor (aka neurofibrosarcoma, malignant schwannoma)	Neurofibromatosis type 1 (Storm et al. 1980; Nambisan et al. 1984; Riccardi and Powell 1989; Rogalski and Louis 1991; Meis et al. 1992; Amir et al. 1993; Matsui et al. 1993)	<i>NF1</i>
	Gastrointestinal	Paraganglioma and gastric sarcoma (Carney and Stratakis 2002) Carney's triad (Valverde et al. 2001; Blei and Gonzalez-Crussi 1992)	<i>SDHB/SDHD</i>
	GIST	GIST (Hirota et al. 2002; Isozaki et al. 2000; Nishida et al. 1998)	<i>KIT, PDGFA</i>
Skin	Melanoma	FAMMM (Lynch et al. 2002; Vasen et al. 2000; Gruis et al. 1995; Lynch and Fusaro 1991)	<i>CDKN2A/p16, CDK4</i>
		Xeroderma pigmentosum (English and Swerdlow 1987; Takebe et al. 1989)	<i>XP-x</i>
		Werner syndrome (Monnat 2002; Goto et al. 1996)	<i>WRN</i>
		Hereditary retinoblastoma (Moll et al. 1997; Eng et al. 1993)	<i>RBI</i>
		Melanoma-astrocytoma syndrome (Randerson-Moor et al. 2001; Bahuau et al. 1998)	<i>CDKN2A/p16, p14ARF</i>
	Nonmelanoma carcinoma	Uveal and cutaneous melanoma	<i>BAP1</i>
		Nevoid basal cell carcinoma (Gorlin) syndrome (Rayner et al. 1977; Gustafson et al. 1989; Gailani and Bale 1997)	<i>PTC</i>
		Xeroderma pigmentosum (Kraemer et al. 1987; Takebe et al. 1989; Cleaver et al. 1981)	<i>XP-x</i>
		Werner syndrome (Zalla 1980; Duvic and Lemak 1995)	<i>WRN</i>
		Fanconi anemia (Somers et al. 1995; Auerbach 1995)	<i>FANC-x</i>
		Bazex–Christol–Dupré syndrome (Gould and Barker 1978; Kidd et al. 1996)	
		Ferguson–Smith syndrome (Bale 1999; Richards et al. 1997; Chakrabarty and Perks 1996)	<i>TGFBRI</i>
		Dyskeratosis congenita (Bale 1999; Richards et al. 1997; Chakrabarty and Perks 1996)	<i>TERC</i> (AD), <i>DKCI</i> (X-linked)
	Squamous cell carcinoma		

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
	Sebaceous carcinoma	Muir–Torre syndrome (Schwartz and Torre 1995; Rutten et al. 1999)	<i>MSH2, MLH1</i>
	Leiomyoma	Multiple leiomyomatosis syndrome (Tomlinson et al. 2002; Jozwiak et al. 1998)	<i>FH</i>
	Angiofibromas facial	Tuberous sclerosis complex (Webb et al. 1996; Sogut et al. 2002; Bellack and Shapshay 1986)	<i>TSC1, TSC2</i>
		MEN 1 (Darling et al. 1997; Marx et al. 1999; Sakurai et al. 2000)	<i>MEN1</i>
	Neurofibroma	Neurofibromatosis type 1 (Szudek et al. 2000; Chung et al. 1999; Friedman and Birch 1997; Goldberg et al. 1996)	<i>NF1</i>
	Trichilemmomas/trichodiscomas/folliculomas	Cowden syndrome (Eng 2000; Starink et al. 1986)	<i>PTEN</i>
		Birt–Hogg–Dube syndrome (Nickerson et al. 2002; Khoo et al. 2001; Ubogy-Rainey et al. 1987)	<i>BHD</i>
Stomach	Carcinoma	HNPCC (Lynch and Lynch 1995; Vasen et al. 1990; Watson and Lynch 1994; Cristofaro et al. 1987; Aarnio et al. 1995)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		Hereditary diffuse gastric cancer syndrome (Shinmura et al. 1999; Guilford et al. 1999; Dunbier and Guilford 2001)	<i>CDH1</i>
		Ataxia telangiectasia (Haerer et al. 1969; Swift et al. 1976; Fraiis 1979)	<i>ATM</i>
		Li–Fraumeni syndrome (Hisada et al. 1998; Varley et al. 1995; Sugano et al. 1999)	<i>TP53</i>
		Juvenile polyposis syndrome (Yoshida et al. 1988; Sassatelli et al. 1993; Hofting et al. 1993; Howe et al. 1998b)	<i>MADH4, BMPRIA</i>
		FAP (Iwama et al. 1993)	<i>APC</i>
		Werner syndrome (Monnat 2002)	<i>WRN</i>
		Hereditary gastrointestinal stromal tumor syndrome (Hirota et al. 2002; Isozaki et al. 2000; Nishida et al. 1998)	<i>KIT, PDGFRA</i>
Testis	Germ cell tumors	Klinefelter syndrome (Aizenstein et al. 1997; Simpson and Photopulos 1976)	<i>XXY</i>

(continued)

**Appendix** (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
		Familial testicular cancer (Cooper et al. 1994; Nicholson and Harland 1995; Heimdal et al. 1996; Rapley et al. 2000)	<i>KITLG, DMRT1</i>
		Carney complex (Carney et al. 1985; Kirschner et al. 2000a; Washecka et al. 2002)	<i>PRKARIA</i>
		Androgen insensitivity (Gourlay et al. 1994; Rutgers and Scully 1991; Cassio et al. 1990; Chen et al. 1999)	<i>AR</i>
		Russell–Silver syndrome (Weiss and Garnick 1981)	
	Sertoli-Leydig cell	DICER syndrome	<i>DICER1</i>
	Gonadoblastoma	WAGR (Pelletier et al. 1991a; Mochon et al. 1987)	<i>WT1</i> , contiguous gene syndrome
Thyroid	Papillary	FAP (Lynch et al. 2001; Iwama et al. 1993; Bell and Mazzaferri 1993; van der Linde et al. 1998; Soravia et al. 1999; Cetta et al. 2000) (see text)	<i>APC</i>
		Cowden syndrome (Eng 2000; Starink et al. 1986; Nelen et al. 1996; Lee et al. 1997; Starink 1984)	<i>PTEN, SDHB, SDHD; KLLN</i> (epimutation)
		Carney complex (Kirschner et al. 2000a; Edwards et al. 2002; Stratakis et al. 1997, 1998)	<i>PRKARIA</i>
		Familial non-medullary thyroid cancer syndromes (Loh 1997; Malchoff and Malchoff 1999; Uchino et al. 2002)	
		Familial papillary thyroid carcinoma (Malchoff et al. 1999; Lupoli et al. 1999; Musholt et al. 2000; Marchesi et al. 2000)	
	Follicular	Cowden syndrome (Eng 2000; Starink et al. 1986; Harach et al. 1999; Kameyama et al. 2001)	<i>PTEN</i>
		Werner syndrome (Monnat 2002; Ishikawa et al. 1999)	<i>WRN</i>
	Medullary	MEN 2 (Eng et al. 1996; Saad et al. 1984; Vasen et al. 1987; Calmettes 1989; Shimotake et al. 1990; Vasen et al. 1992; Iihara et al. 1997)	<i>RET</i>

Appendix (continued)

Organ or neoplasia type	Histological type	Genetic differential diagnosis	Gene (if known)
Uterus	Endometrial carcinoma	HNPCC (Watson and Lynch 1993; Brown et al. 2001; Vasen et al. 1990; Mecklin and Jarvinen 1991; Watson et al. 1994; Wijnen et al. 1998; Weber et al. 1999; Peel et al. 2000)	<i>MLH1, MSH2, MSH6, PMS1, PMS2</i>
		Cowden syndrome (Eng 2000; Starink et al. 1986; Marsh et al. 1998)	<i>PTEN</i>
	Myometrial leiomyoma	Cowden syndrome (Eng 2000; Starink et al. 1986; Marsh et al. 1998) Multiple leiomyomatosis–renal cell cancer (Kiuru et al. 2001; Tomlinson et al. 2002; Launonen et al. 2001)	<i>PTEN</i> <i>FH</i>
Vulva	Squamous cell	Fanconi anemia (Wilkinson et al. 1984; Kennedy and Hart 1982)	<i>FANC-x</i>

<sup>a</sup>To add to Emberger Syndrome: Ostergaard et al. (2011)

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# Index

## A

- Acoustic neuroma, 2
- ACTH-independent Cushing's syndrome, 203
- Acute lymphoblastic leukemia (ALL)
  - description, 146
  - familial clustering, adult, 147
  - genetic disorders and childhood leukemia, 147
  - heterogeneous disorder, 146
  - immunological classification, 146–147
- Acute myeloid (myelogenous) leukemia (AML)
  - autosomal dominant condition
    - characterization, 148
  - bone marrow monosomy 7, 147
  - CEBPA mutation and RUNX1, 148
  - description, 147
  - Down syndrome and true nonsyndromic familial, 147
  - hematologic characteristics, 148
  - homozygous/monoallelic germline inactivating mutations,
    - EZH2, 148
  - Prader–Willi syndrome and erythroleukemia, 148
- Adenocarcinoma. *See* Renal cell carcinoma (RCC)
- Adrenal gland tumors
  - clinical algorithm, 37, 38
  - clinical surveillance, 38
  - extra-adrenal (chromaffin) paragangliomas, 36
  - genetic differential diagnosis, 36
  - genetic testing algorithm, 37
  - germline mutations, 36
  - MEN 2-related, 38
  - non-syndromic, 37
  - and paraganglioma presentations, 37
  - sample surveillance protocol, SDH mutation carrier, 39
  - somatic VHL, RET and SDHD mutations, 38
- Adrenocortical adenoma and carcinoma
  - benign/malignant, 39
  - germline *TP53* mutations, 39
  - germline variation, *PDE11*, 40
  - hypercortisolism, 40
  - nodular hyperplasia, 39–40
  - PPNAD, 39
- Albinism
  - complications, 192
  - cutaneous malignancies, 192
  - oculocutaneous, 192
- ALL. *See* Acute lymphoblastic leukemia (ALL)
- Altieri, A., 154
- AML. *See* Acute myeloid (myelogenous) leukemia (AML)
- Anhydrotic ectodermal dysplasia, 195
- Astrocytoma. *See* Gliomas
- Ataxia telangiectasia
  - acanthosis nigricans, 219
  - ATM* gene, 220
  - lymphoreticular neoplasms, 219–220
- Ataxia-telangiectasia-like disorder (ATLD)
  - Arg202Gly, 221
  - MRE11 gene, 220
- ATLD. *See* Ataxia-telangiectasia-like disorder (ATLD)
- Autosomal recessive childhood cancer predisposition syndrome, 232

**B**

- Bannayan–Riley–Ruvalcaba syndrome (BRRS)  
     medical management, 221  
     *PTEN* mutations, 221
- Basal cell carcinoma (BCC)  
     after radiotherapy, 186  
     epithelial tumor and lifetime risk, 185  
     genetic disorders, 186–187  
     “patched” *PTCH1* gene, 186–187  
     polymorphisms and melanoma, 186  
     red-haired individuals, 186  
     registry-based study and  
         arsenic, 185–186
- Bazex–Dupre–Christol syndrome  
     basal cell nevus syndrome, 188  
     BCC, 188  
     follicular atrophoderma (ice pick marks), 1  
     hair follicle, 188  
     milia, dorsa, 187, 188  
     trichoepitheliomas, 188  
     X-linked dominant trait, 188
- BCC. *See* Basal cell carcinoma (BCC)
- BCR. *See* Breakpoint cluster region (BCR)
- Beckwith–Wiedemann syndrome (BWS)  
     *CDKN1C* mutations, 223–224  
     characterization, 222  
     chromosomal rearrangements, 223  
     chromosome 11p15.5, 223  
     diagnosis, 222  
     genotype-phenotype correlations, 224  
     hemihypertrophy and neoplasia, 224  
     sporadic Wilms tumors, 139
- Benign neoplasia, thyroid tumors, 34
- Bertola, D.R., 230
- BHD. *See* Birt–Hogg–Dubé syndrome (BHD)
- Birt–Hogg–Dubé syndrome (BHD)  
     autosomal dominant condition, 192  
     chromophobe–oncocyoma  
         appearance, 140  
     fibrofolliculomas, 224–225  
     RCC, 225  
     renal tumors, 225
- Blackfan–Diamond anemia (DBA), 226
- Bladder cancer  
     carcinoma, 142  
     environmental factors, 142  
     familial clusters, 142  
     genetic factors, 142  
     SNPs, 142  
     synchronous/metachronous, 142–143  
     urine sediment analysis, 143
- Blattner, W.A., 158
- Bloom syndrome  
     BLM protein levels, 227  
     cervical screening, 226  
     characterization, 226  
     colorectal cancer, 226–227  
     registry, 227
- Blue rubber bleb nevus syndrome, 227–228
- Bone tumors  
     age-standardized rate, 167  
     osteosarcoma (*see* Osteosarcomas)
- Bourdeaut, F., 8, 9
- BRCA1 and BRCA2 genes  
     BOADICEA and BRCAPRO, 97  
     epidemiological data, 96  
     familial aggregation, 95  
     genes and risks  
         and binding partners, 92, 93  
         description, 91  
         diagnosis, women, 93  
         mutations, 93  
         non-breast/ovary sites by age of  
             onset, 91, 93  
         RR estimation, mutation carriers, 91  
         susceptibility, 91  
     germline TP53 mutations, 96  
     “moderate-penetrance”, 95–96  
     protein function  
         cells defective, 94  
         E3 ubiquitin ligase activity, 94  
         mutation, carriers vs. noncarriers, 94  
         PARPi, 95  
         repair, double-strand DNA breaks,  
             93–94  
         tumor suppression, 94  
     PTEN, STK11 and CDKN2A, 96  
     truncating somatic mutations, *PPM1D*, 96
- Breakpoint cluster region (BCR), 149
- Breast cancer  
     BRCA1 and BRCA2 (*see* BRCA1 and  
         BRCA2 genes)  
     epidemiology and family history  
         “breast/colorectal” families, 90  
         cumulative incidence, 90  
         mammographic detection, ductal  
             carcinoma, 89  
         non-cutaneous, women, 89  
         relative risk (RR), 90  
         RR estimation, mutation carriers, 91  
         twin studies, 89  
     genetic counseling  
         BRCA1/BRCA2 germline  
             mutations, 98  
         family history, 98  
     IBIS and BRCAPRO programs, 98  
     prophylactic and surveillance  
         interventions, 98–99

- psychological impact, 99
  - "risks of knowledge" and negative effects, 99
  - histopathology and genetics
    - relationship, 97
  - prophylaxis, 100–101
  - screening, 99–100
- Brooke–Spiegler syndrome, 192–193
- BRRS. *See* Bannayan–Riley–Ruvalcaba syndrome (BRRS)
- Burkland, C.E., 142
- Burt, R.D., 26
- BWS. *See* Beckwith–Wiedemann syndrome (BWS)
- C**
- Cairns, S.R., 70, 71
- Cancers
  - bladder, 142–143
  - ureter and renal pelvis, 141–142
- Canning, C.R., 21
- Carcinomas
  - ovarian cancer
    - BRCA1* and *BRCA2* mutations, 107, 108
    - CA-125, 111–112
    - chemotherapeutic agents, 111
    - family history, ovarian neoplasia, 107
    - Fanconi anemia genetic pathway, 110
    - founder populations, 107
    - genotype–phenotype relationships, 108
    - gynecological malignancies, 105
    - histopathological analysis, prophylactic oophorectomy, 108–109
    - Lynch syndrome, 110–111
    - malignant transformation, 110
    - MLH1* and *MSH2* mutations, 110
    - OCCR and non-OCCR, 108
    - prophylactic salpingo-oophorectomy, 111
    - risk in women with family history of OC, 108, 109
    - serous papillary cystadenocarcinoma, 107
    - sporadic, 110
    - therapeutic effectiveness, PARP inhibitors, 111
  - uterus
    - cancer-dense pedigrees, 103
    - clinical surveillance, malignancies, 103–104
    - endometrioid endometrial, 103
    - epidemiological studies, 102
    - 113 families, *MSH6* mutations, 102
    - female mutation carriers, 102–103
    - histological types, 102
    - immunohistochemistry, MMR proteins, 103
    - MLH1* and *MSH2* carriers, 103
- Cardiac tumors, 28–29
- Cardio-cutaneous-facial syndromes, 171
- Cardiorespiratory system and thorax
  - cardiac tumors, 28–29
  - head and neck cancer, 25–26
  - larynx, 26
  - lung cancer, 27–28
  - mesothelioma, 28
  - nasopharynx, 26
  - thymomas, 26
- Carney complex (CNC)
  - ACTH-independent Cushing's syndrome, 203
  - clinical and biochemical screening, 229
  - description, 228–229
  - endocrine neoplasia and lentiginosis syndrome, 203
  - mutations, *PRKRI1A*, 229
  - PRKRI1A* gene, 203
  - testicular ultrasonography, 230
- Carney, J.A., 28
- Carney–Stratakis syndrome (CSS), 228
- Cavernous hemangioma, 20
- CDKN2A* mutations
  - breast cancer and germline mutations, 182
  - CDKN2A5* UTR and *CDK4* gene, 183
  - chromosome 9 and 22, 179
  - GenoMEL and mutation carriers, 181
  - polymorphism Ala148Thr, 184
  - screening, pancreatic cancer, 184
  - tumor suppressor gene, 182
- Celiac disease, 231
- Central nervous system (CNS)
  - choroid plexus tumor, 2–3
  - ependymoma, 3
  - genetic disorders, 1, 2
  - gliomas, 3–4
  - hemangioblastoma, 4–5
  - hemangioma, 5
  - medulloblastoma, 5–6
  - meningioma, 6
  - nerve root tumors, 6–7
  - neuroblastoma, 7–8
  - neurofibromatosis, 1
  - pineal tumor, 8
  - PNETs, 8–9
  - soft tissue sarcomas and brain tumors, 1
  - vestibular schwannoma (acoustic neuroma), 2

- Cerebro-oculo-facio-skeletal (COFS), 231
- Cervix cancer
- carcinoma, uterine, 113
  - cigarette smoking-associated cancers, 113
  - E6 and E7 viral proteins, 113
  - embryonal tumors, 113
  - family history studies, women, 113
  - host factors, 113
  - primary melanoma, 113
- Cheilitis glandularis, 193
- Chemoprophylaxis
- CAPP2, 71–72
  - COX-2 inhibitors, 71
  - fish oils, 72
- Chen, J.D., 267
- Choi, N.W., 1
- Cholangiocarcinoma, liver, 56
- Chondrosarcoma
- description, 169
  - hereditary multiple exostoses, 170
  - intracranial chordoma, 170
  - Maffucci syndrome, 170
  - Ollier disease, 169
  - sarcomatous degeneration, 170
- Choriocarcinoma, uterine tumors, 104
- Choroid plexus tumor, 2–3
- Chronic lymphocytic leukemia (CLL)
- acute leukemia and CML, 149
  - ALL and TMD, 151
  - B cell type, 149
  - and CBL, 151
  - children with DS, 151–152
  - disordered immune function and lymphoreticular malignancy, 149
  - down syndrome and Legius syndrome, 151
  - familial cases, 150
  - familial clustering, hairy cell leukemia, 150
  - germline mutations in DAPK1, 150
  - and JMML, 151
  - loss-of-function polymorphism, cytolytic P2X7 receptor gene, 149
  - low-penetrance risk alleles and lymphoproliferative disease, 150
  - monoclonal blood B lymphocyte population, 149–150
  - non-DS patients, 152
  - somatic inactivation, ataxia-telangiectasia gene, 150
  - subclinical levels, 150
- Chronic mucocutaneous candidiasis syndrome
- CANDF2, 193
  - Candida* endocrinopathy syndrome, 193
  - germline mutation in *AIRE*, 193
  - ICAM-1 deficiency, 194
  - vertical transmission, 193
- Chronic myeloid leukemia (CML)
- BCR*, 149
  - environmental agents, 149
  - malignant transformation, pluripotent bone marrow stem cell, 148–149
  - Philadelphia (Ph) chromosome, 149
- Clementi, R., 154, 157
- Clericuzio, C.L., 255
- CLL. *See* Chronic lymphocytic leukemia (CLL)
- Clouston syndrome, 195
- CML. *See* Chronic myeloid leukemia (CML)
- CMMRD. *See* Constitutional mismatch repair deficiency (CMMRD)
- CNC. *See* Carney complex (CNC)
- CNS. *See* Central nervous system (CNS)
- Cockayne syndrome
- COFS, 231
  - CS-B gene product, 230
- COFS. *See* Cerebro-oculo-facio-skeletal (COFS)
- Cohen, A.J., 140
- Colorectal cancer (CRC)
- causes, cancer death, 63
  - colorectal polyposis, 64, 65
  - exons of *EPCAM*, 66
  - familial adenomatous polyposis, 65
  - familial giant hyperplastic polyposis coli, 64–65
  - family history and risk of death, 64
  - genetic factors, 64
  - germline *BRCA1* mutations, 67
  - germline *PTEN* mutations, 65
  - HNPCC, 66
  - identification, high-risk families, 67–69
  - inflammation, 64
  - MLH3* and *EXO1*, 65
  - NAT2 and metabolic gene variants, 67
  - pathogenic *APC* and biallelic *MUTYH* mutations, 66–67
  - pathological features, 69
  - surveillance strategies, 69–71
- Common variable immunodeficiency (CVID), 232
- Congenital generalized fibromatosis, 194
- Constitutional mismatch repair deficiency (CMMRD), 232
- Contiguous gene syndrome, 169
- Core-binding transcription factor (CBF), 148
- Costello syndrome, 232–233
- Cowden syndrome (CS)
- breast and epithelial carcinoma, 234–235
  - colon cancer, 238
  - diagnostic criteria, 233
  - endometrial carcinoma, 236

- hamartomatous polyps, 236
  - mTOR inhibitors, 238
  - mutations, *PTEN*, 95, 233, 237, 238
  - operational criteria, 233–234
  - renal tumors, 141
  - thyroid carcinoma, 233–234
  - CRC. *See* Colorectal cancer (CRC)
  - CS. *See* Cowden syndrome (CS)
  - CSS. *See* Carney–Stratakis syndrome (CSS)
  - CVID. *See* Common variable immunodeficiency (CVID)
- D**
- Davies, H.D., 148
  - DBA. *See* Blackfan–Diamond anemia (DBA)
  - Delleman, J., 6
  - Denys–Drash syndrome
    - Wilms' tumor, 240
    - WT1* gene product, 138, 252
  - Dermatological malignancy
    - albinism, 192
    - Birt–Hogg–Dubé syndrome, 192
    - Brooke–Spiegler syndrome, 192–193
    - cheilitis glandularis, 193
    - chronic mucocutaneous candidiasis syndrome, 193–194
    - congenital generalized fibromatosis, 194
    - dyskeratosis congenita, 194–195
    - ectodermal dysplasias, 195
    - epidermolysis bullosa, 195–196
    - flegel disease, 197
    - juvenile hyaline fibromatosis, 197
    - KID syndrome, 196–197
    - Klippel–Trenaunay syndrome, 198
    - lichen planus, 198
    - lichen sclerosis et atrophicus, 201
    - mast cell disease, 201
    - mibelli porokeratosis, 198
    - multiple cutaneous leiomyomas, 201–202
    - multiple cylindromatosis, 197
    - multiple lipomatosis
      - familial, 202
      - symmetric, 202–203
    - NAME syndrome, 203
    - palmar keratoses, 204
    - PC, 203–204
    - pilomatrixoma, 204
    - proteus syndrome, 199
    - sclerolytosis, 199
    - steatocystoma multiplex, 200
    - syringomas, 200
    - trichoepithelioma, 200
    - tylosis, 200
  - De Sanctis–Cacchione syndrome, 321
  - Diffuse large B cell lymphoma (DLBCL), 157
  - DLBCL. *See* Diffuse large B cell lymphoma (DLBCL)
  - Down syndrome (DS)
    - acute megakaryoblastic leukemia, 151
    - description, 240
    - DS-AMKL harbor mutations, 240–241
    - genetic disorders, 143
    - JAK2R683* mutations, 241
  - Draper, G.J., 16, 17
  - Draptchinskaia, N., 226
  - DS. *See* Down syndrome (DS)
  - Dyskeratosis congenita
    - D9S52, 195
    - female carriers, 194
    - hematopoietic stem cell transplantation, 194
    - immune dysfunction, 194
    - leukoplakia and X-linked condition, 194
    - SCC, 194
- E**
- Ectodermal dysplasias, 195
  - Elliott, M.L., 222
  - Ellis, N.A., 226
  - ELSTs. *See* Endolymphatic sac tumors (ELSTs)
  - Endocrine system
    - adrenal gland tumors, 36–39
    - adrenocortical adenoma and carcinoma, 39–40
    - glomus tumors, 40–41
    - pancreatic, 41
    - parathyroid tumors (*see* Parathyroid tumors)
    - pituitary tumors (*see* Pituitary tumors)
    - thyroid tumors (*see* Thyroid tumors)
  - Endolymphatic sac tumors (ELSTs), 313
  - Endometrial cancer
    - aspirin, 264
    - characteristics, 263
    - description, 263–264
    - genetic counseling, Lynch syndrome, 265–266
    - screening, 263–265
  - Eng, C., 17, 35
  - Ependymoma
    - CNS tumors, 293
    - NF2, 3
  - Epidermodysplasia verruciformis (EV)
    - EVER proteins, 190
    - HIV-positive patients, 190
    - and HPV, 190



- Epidermolysis bullosa  
 autosomal dominant Dowling-Meera form, 195–196  
 classification, 195  
 dystrophic, 196  
 germline mutations, 196  
 heterogeneous group, inherited disorders, 195  
 SCC, 189  
 simplex forms, 196
- Epididymal tumors, 121
- EPOR. *See* Erythropoietin receptor (EPOR)
- Epstein–Barr virus (EBV) infection, 155
- Erythropoietin receptor (EPOR), 148
- Esophageal tumors  
*BRCA2* gene, 48–49  
 germline mutations, *MSR1*, 49  
 high-incidence regions, 48  
 late-onset tylosis, 49  
 prophylactic esophagectomy, 49  
 risks, 49  
 squamous cell carcinoma, 48
- EV. *See* Epidermodysplasia verruciformis (EV)
- Evans, D.G.R., 293, 294
- Ewing sarcoma  
 neuroectodermal tumors, 167  
 retinoblastoma, 170
- Exostoses-anetoderma-brachydactyly type E, 169
- External genitalia cancer, 114
- Extraskeletal myxoid chondrosarcomas, 172
- Eye  
 cavernous hemangioma, 20  
 hemangioblastoma, 20–21  
 melanoma, 21–22  
 meningioma, 22  
 ocular choristoma, 20  
 optic glioma, 19  
 retinal astrocytic hamartoma, 19  
 retinoblastoma, 15–19
- F**
- FA. *See* Fanconi anemia (FA)
- Fallopian tube carcinoma  
*BRCA1/2* mutations, 101–102  
 genetic disorders, ovarian neoplasms, 106, 113  
 Lynch syndrome, 105
- Familial adenomatous polyposis (FAP)  
 age-related carrier risk, 242  
*APC* gene, 242–243  
 and CHRPEs, 241–242  
 depigmentation, 242  
 desmoid disease, 244  
 diagnosis, 241  
 extraintestinal lesions, 241–242  
 MUTYH, biallelic mutations, 241  
 polymorphism, 245  
 polyps, 236  
 predictive test, 245  
 proctocolectomy, 246–247  
 spigelman score, duodenal polyposis, 248  
 thyroid gland, 247
- Familial hemophagocytic lymphohistiocytosis (FHL), 154
- Familial medullary thyroid carcinoma (FMTC), 283
- Familial melanoma  
 AMS and genetic linkage, 181  
*CDK4*, 183–184  
*CDKN2A* (*see CDKN2A* mutations)  
 description, 180–181  
 EUROPAC and ankyrin repeats, 184  
 gene testing, 184  
 GenoMEL, 184  
 germline mutations, 187–188  
 nodular, lentigo maligna and ocular melanomas, 181  
*p14ARF* and *BAP-1*, 183  
 p16-Leiden families, 182  
 screening, nevi, 181
- Fanconi anemia (FA)  
 birth incidence, 249  
 chromosomal hypersensitivity, DNA, 249–250  
*FANCA* mutations, 250  
 hematologists, 251  
 pancytopenia, 249  
*XRCC2* mutations, 244
- FAP. *See* Familial adenomatous polyposis (FAP)
- Ferguson-Smith-type self-healing epithelioma  
 anal tumors and SCC, 191  
 keratoacanthomas, 190, 191  
*TGFBR1*, 191
- Ferraris, A.M., 155
- FH. *See* Fumarate hydratase (FH)
- FHL. *See* Familial hemophagocytic lymphohistiocytosis (FHL)
- Flegel disease, 197
- Fletcher, O., 17
- FMTC. *See* Familial medullary thyroid carcinoma (FMTC)
- Follicular thyroid carcinoma (FTC)  
 microarray expression strategies, 33  
 PTEN-related CS and Werner syndrome, 33  
 somatic *PAX8/PPARG* translocations, 33

- Foster, C.B., 172  
 Frasier syndrome, 252  
 Fraumeni, J.F., 142  
 FTC. *See* Follicular thyroid carcinoma (FTC)  
 Fumarate hydratase (FH), 202
- G**
- Gallbladder tumors, 57  
 Gastric carcinoma  
   adenocarcinoma, stomach, 52  
   breast cancer, 52–53  
   *CDH1* mutations, 52–53  
   chronic atrophic gastritis, 51  
   HDGC, 52  
   histological variants, 51  
   Lynch syndrome, 51–52  
   risks, 52–53  
 Gastric tumors  
   diagnosis, GAPPs, 50  
   fundic gland polyposis and intestinal-type gastric cancer, 50  
   hyperplastic gastric polyps, 50  
   polypliod adenomas, 50  
 Gastrointestinal polyposis  
   conditions associated with, 62  
   Cronkhite-Canada syndrome, 62  
   germline mutations, *SMAD4/BMPRIA*, 63  
   hereditary mixed, 63  
   juvenile, 63  
   small rectal hamartomatous, 63  
 Gastrointestinal system  
   chemoprophylaxis, 71–72  
   cholangiocarcinoma, liver, 56  
   colon and rectum tumors (*see* Colorectal cancer (CRC))  
   esophageal tumors, 48–49  
   gastric carcinoma, 51–53  
   gastric tumors, 49  
   hepatic angiosarcoma, 56  
   hepatic tumors (*see* Hepatic tumors)  
   management, 49  
   pancreatic cancer, 57–60  
   polyposis (*see* Gastrointestinal polyposis)  
   salivary gland tumors, 47–48  
   small intestines (*see* Small intestine tumors)  
   tumors, gallbladder, 57  
 Genetic differential diagnoses, 361–377  
 Giant congenital melanocytic nevus, 185  
 Glioblastoma. *See* Gliomas  
 Gliomas  
   astrocytoma and glioblastoma, 3–4  
   candidate gene analysis, 4  
   GLIOGENE consortium, 4  
   monozygotic twins, 3–4  
   submicroscopic germline deletions, 9p21, 4  
 Glomus tumors  
   bilateral disease, 40  
   chemodectomas, 40  
   germline mutations, *SDHD*, 40  
   germline *TMEM127*, 40  
   head and neck paragangliomas, 40–41  
 Glutathione S transferase M1 (GSTM1)  
   genotype, 27  
 Gold, E.B., 1  
 Gomez, M.R., 308  
 Gorlin, R.J., 27  
 Gorlin syndrome  
   BCC, 252  
   description, 186  
   diagnostic criteria, 254  
   genetic counseling, 254  
   *PTCH* inhibition, 255  
   seminoma, 254  
 GSTM1 genotype. *See* Glutathione S transferase M1 (GSTM1) genotype  
 Gustavsson, P., 220
- H**
- Hashmi, S.K., 306  
 HDGC. *See* Hereditary diffuse gastric cancer (HDGC)  
 Head and neck cancer, 25  
 Hemangioblastoma  
   estimated probability, VHL, 21  
   false-negative mutation analysis results, 5  
   molecular studies, 21  
   retinal, 21  
   VHL disease, 4  
 Hemangioma, 5  
 Hemminki, K., 157  
 Hemophagocytic lymphohistiocytosis (HLH), 157  
 Henneveld, H.T., 3  
 Hepatic angiosarcoma, 56  
 Hepatic tumors  
   hepatoblastoma, 53  
   hepatocellular carcinoma, 53–56  
 Hepatoblastoma  
   extraintestinal cancers, 244  
   hepatic tumors, 53  
   and nephroblastomatosis, 298

Hepatocellular carcinoma  
 $\alpha$ -1 antitrypsin deficiency, 55  
 genetic causes, liver cancer, 54  
 glycogen storage disease, 55  
 hepatic porphyrias, 55  
 hepatitis B viral infections and  
 aflatoxin, 53  
 hepatoma, 55  
*HFE* mutations, 54  
 intra-abdominal malignancy, 55  
 marked geographical variations, 53–54  
 MODY type 3, 56  
 neonatal giant cell hepatitis, 56  
 Werner syndrome, 55

Hereditary diffuse gastric cancer (HDGC), 52

Hereditary leiomyoma–renal cell carcinoma  
 syndrome (HLRCC)  
 germline heterozygous mutations, 102  
 uterine leiomyomas, 101–102

Hereditary non-polyposis colon (colorectal)  
 cancer (HNPCC)  
 bladder cancer, patients, 142–143  
 clinical features and pathology, 257–258  
 diagnostic features, 258–261  
 familial clustering, 57  
 gastric carcinoma, 52  
 history and epidemiology, 256–257  
 Lynch syndrome, 65  
 molecular genetics, 261–262  
 ureter and renal pelvis, 142

HHV8. *See* Human herpes virus 8 (HHV8)

Histiocytoses  
 FHL, 159  
 hemophagocytic syndromes, 159  
 LCH, 158–159

HL. *See* Hodgkin disease (HL)

HLH. *See* Hemophagocytic  
 lymphohistiocytosis (HLH)

HLRCC. *See* Hereditary leiomyoma–renal cell  
 carcinoma syndrome (HLRCC)

HNPCC. *See* Hereditary non-polyposis colon  
 (colorectal) cancer (HNPCC)

Hodgkin disease (HL)  
 bimodal distribution, 154  
 chromosomal rearrangements, 155–156  
 etiology and EBV infection, 155  
 familial clustering and HLA loci, 156  
 genetic and environmental factors, 156  
 germline mutations in NPAT, 156  
 JAK inhibitors, 155–156

Horwitz, L.J., 157

Horwitz, M., 147, 148

Houdayer, C., 18

Houlston, R.S., 64

Hovhannisyann, Z., 231

HPT-JT. *See* Hyperparathyroidism–jaw tumor  
 syndrome (HPT-JT)

Human herpes virus 8 (HHV8), 172

Hungerford, J., 21

Huson, S.M., 289–291

Hyperkeratosis lenticularis perstans, 197

Hypernephroma. *See* Renal cell carcinoma  
 (RCC)

Hyperparathyroidism–jaw tumor syndrome  
 (HPT-JT)  
*CDC73* mutations, 267  
 description, 266  
 parathyroid disease, 267  
 renal tumors, 140

## I

Inherited cancer-predisposing syndromes  
 ataxia telangiectasia, 219–220  
 ATLD, 220–221  
 BHD syndrome, 221  
 Bloom syndrome, 226–227  
 Blue rubber bleb nevus syndrome,  
 227–228  
 BRRS, 221  
 BWS, 211–224  
 celiac disease, 231  
 CMMRD, 232  
 CNC, 228–230  
 Cockayne syndrome, 30–231  
 Costello syndrome, 232–233  
 CS, 233–239  
 CSS, 228  
 CVID, 232  
 DBA, 225–226  
 Denys–Drash syndrome, 239–240  
 DS, 240–241  
 endometrial cancer, 262–266  
 FA, 249–251  
 FAP, 241–249  
 Frasier syndrome, 252  
 Gorlin syndrome, 252–255  
 hemihypertrophy/hemihyperplasia, 255  
 HNPCC, 255–262  
 HPT-JT, 266–267  
 JPS, 267–269  
 Klinefelter syndrome, 270  
 Kostmann syndrome, 270–271  
 LFS, 271–274  
 Maffucci syndrome, 274–275  
 MAP, 287–288  
 MAS, 275–276  
 MEN 2, 281–286  
 MEN1 and *CDKN*-opathies, 278–281  
 Muir–Torre syndrome, 286–287

- MVA, 277  
 NBS, 296–297  
 NF1, 288–296  
 Noonan syndrome, 297–298  
 N syndrome, 288  
 Perlman syndrome, 298  
 PJS, 299–301  
 porphyria, 302–303  
 PPB-FTDS, 301–302  
 rhabdoid tumors, 303–304  
 Rothmund–Thomson syndrome, 304  
 SCID, 305  
 Shwachman–Diamond syndrome, 305–306  
 Simpson–Golabi–Behmel syndrome, 306  
 Sotos syndrome, 307  
 TS, 312  
 tuberose sclerosis, 307–310  
 Turcot syndrome, 311–312  
 tylosis, 312–313  
 VHL syndrome, 313–317  
 WAS, 319–320  
 Werner syndrome, 318–319  
 xeroderma pigmentosum, 320–322  
 X-linked lymphoproliferative disorder, 320
- J**
- JMML. *See* Juvenile myelomonocytic leukemia (JMML)  
 JPS. *See* Juvenile polyposis syndrome (JPS)  
 Juvenile hyaline fibromatosis, 197  
 Juvenile myelomonocytic leukemia (JMML), 151  
 Juvenile polyposis syndrome (JPS)  
   BMP pathway, 268  
   cancer genetic consultation, 267, 269  
   diagnosis, 267–268  
   histopathology, 268  
   SMAD4 mutations, 268  
 Juzek, R.H., 142
- K**
- Kanter, W.R., 293, 294  
 Kaposi sarcoma (KS), 172  
 Kauppinen, R., 302  
 Keratitis, ichthyosis and deafness (KID) syndrome, 196–197  
 Kibirige, M.S., 3  
 KID. *See* Keratitis, ichthyosis and deafness (KID) syndrome  
 Kikuchi, M., 153  
 Klinefelter syndrome  
   cancer, 270  
   description, 270  
   extragonadal malignant germ cell tumors, 270  
 Klippel–Trenaunay syndrome, 198  
 Knudson, A.G., 7  
 Kostmann syndrome, 270–271  
 KS. *See* Kaposi sarcoma (KS)  
 KS-associated herpes virus (KSHV), 172  
 KSHV. *See* KS-associated herpes virus (KSHV)
- L**
- Langer–Giedion syndrome, 169  
 Langerhans cell histiocytosis (LCH), 158–159  
 Larynx  
   cigarette smoking-associated cancers, 113  
   description, 26  
   Muir–Torre syndrome, 286–287  
   neoplasms, 226  
   squamous carcinomas, head and neck, 25  
 LCH. *See* Langerhans cell histiocytosis (LCH)  
 Leachman, S.A., 184  
 Legius syndrome, 151  
 Leiomyoma, uterine tumors  
   Afro-Caribbean origin, 101  
   HLRCC/MCUL and Cowden syndrome, 101–102  
   PTEN and SDHC, 102  
 Leukemia  
   ALL, 146–147  
   AML, 147–148  
   CLL, 149–152  
   CML, 148–149  
   description, 145  
   environmental factors, 146  
   genetic disorders, 146  
   genome-wide association studies, 146  
   polycythemia, 152–153  
   thrombocythemia, 153  
 Lewis, R.A., 291  
 LFS. *See* Li–Fraumeni syndrome (LFS)  
 Lichen planus, 198  
 Lichen sclerosis et atrophicus  
   dermatological disorder, 201  
   extragenital lesions, 201  
   p53 levels and 17p, LOH, 201  
 Li–Fraumeni syndrome (LFS)  
   ACC, 273  
   clinical features, 271–272  
   genetic and medical management, 274  
   genotype-phenotype correlations, 273  
   operational diagnostic criteria, 271  
   osteogenic sarcoma, 168  
   TP53 mutations, 272

- Li, M., 306
- Lohmann, D.R., 17
- Lung cancer
- adenocarcinoma and alveolar cell carcinoma, 27
  - familial clustering, 27
  - genome-wide association, 27–28
  - GSTM1, 27
- Lymphoma
- genetic disorders, 154
  - HL, 154–156
  - HLH, 154
  - lymphoproliferative disorders, 154
  - NHL, 157
- Lynch, H.T., 142, 156, 158, 256
- Lynch syndrome
- endometrial cancer, 262–266
  - HNPCC, 256–262
  - “MMR” genes, 154
- M**
- Maffucci syndrome
- chondrosarcoma, 274
  - description, 274
  - IDH1/IDH2*, 274–275
  - multiple enchondromas and subcutaneous hemangiomas, 170
- Mahaley, M.S., 1
- Maher, E.R., 222
- Malignant rhabdoid tumor (MRT), 172
- Manski, T.J., 317
- MAP. *See* MUTYH-associated polyposis (MAP)
- Martin, R.A., 140
- MAS. *See* McCune–Albright syndrome (MAS)
- Mast cell disease, 201
- McCullough, D.L., 142
- McCune–Albright syndrome (MAS)
- fibrous dysplasia, 275
  - GNAS1* gene, 276
  - osteosarcomatous transformation, 276
  - POFD, 275
- McLaughlin, J.K., 140
- Medullary thyroid carcinoma (MTC)
- etiology, sporadic, 33
  - MEN 2 susceptibility gene, 33
  - somatic RET mutations, 33–34
- Medulloblastoma
- cancer genome analysis, 6
  - familial, 5
  - Gorlin syndrome, 5
  - patients with homozygous *BRCA2* mutations, 5
- Melanoma
- AMS, 179
  - ARNT*, 180
  - familial (*see* Familial melanoma)
  - germline BAP1 mutations, 22
  - GWAS, 179, 180
  - Li–Fraumeni syndrome and retinoblastoma, 180
  - MC1R*, 180
  - non-polyposis colorectal cancer and congenital anomalies, 180
  - Scandinavian families and clustering, 180
  - sex difference, 178
  - SNPs and “skin type”, 179
  - somatic mutations, 22
  - superficial spreading type and prognosis, 178
  - TERF*, 179
  - uveal, 21
  - white and pigmented skins, 178
- MEN1. *See* Multiple endocrine neoplasia type 1 (MEN1)
- MEN 2. *See* Multiple endocrine neoplasia type 2 (MEN 2)
- Meningioma, 6, 22
- Mesothelioma, 28
- Miller, R.W., 1
- MM. *See* Multiple myeloma (MM)
- Moll, A.C., 17
- Morison, I.M., 224
- Mosaic variegated aneuploidy (MVA)
- biallelic mutations, 277
  - BUB1B, mutations, 277
  - description, 277
- MRT. *See* Malignant rhabdoid tumor (MRT)
- MTC. *See* Medullary thyroid carcinoma (MTC)
- Muir–Torre syndrome
- description, 286
  - FHIT protein, 287
  - mutations, MMR genes, 286
- Multiple cutaneous leiomyomas, 201–202
- Multiple cutaneous uterine leiomyomatosis (MCUL). *See* Hereditary leiomyoma–renal cell carcinoma syndrome (HLRCC)
- Multiple cylindromatosis, 192–193, 197
- Multiple endocrine neoplasia type 1 (MEN1)
- clinical features, 278
  - genetics, 279
  - germline mutations, 278
  - medical management, 280–281
- Multiple endocrine neoplasia type 2 (MEN 2)

- and ACTH, 282
    - description, 281
    - and FMTC, 283
    - medical management, 285–286
    - molecular genetics, 283–284
    - and MTC, 281
    - mucosal neuromas, 283
  - Multiple lipomatosis
    - familial, 202
    - symmetric, 202–203
  - Multiple myeloma (MM)
    - description, 157, 158
    - monoclonal gammopathy, 158
    - plasma cell disorders, 157–158
  - Musculoskeletal system, bone tumors.
    - See* Bone tumors
  - MUTYH-associated polyposis (MAP), 287
  - MVA. *See* Mosaic variegated aneuploidy (MVA)
- N**
- NAME syndrome. *See* Carney complex
  - Nasopharynx
    - in head and neck cancer, 26
    - squamous carcinomas, 25
  - Naumova, A., 16
  - NBS. *See* Nijmegen breakage syndrome (NBS)
  - Nerve root tumors, 6–7
  - Neumann, H.P.H., 20
  - Neuroblastoma, 7–8
  - Neurofibromatosis type 1 (NF1)
    - CNS tumors, 290
    - dermal, 290, 291
    - diagnosis, 289
    - endocrine tumor, 292
    - nonneoplastic complications, 288
    - optic glioma, 291
    - plexiform, 290
    - presymptomatic diagnoses, 292
    - tumor types, 290
  - Neurofibromatosis type 2 (NF2)
    - chromosome 22, 295
    - classification, 295
    - clinical features, 293
    - diagnostic criteria, 293, 294
    - evidence, 294
    - mutation, blood, 295
    - prognosis, 296
    - proportion, 294
  - Newton-Bishop, J.A., 177
  - NF1. *See* Neurofibromatosis type 1 (NF1)
  - NHL. *See* Non-Hodgkin lymphoma (NHL)
  - Nicodème, F., 26
  - Nijmegen breakage syndrome (NBS),
    - 296–297
  - Non-chromaffin paraganglioma. *See* Glomus tumors
  - Non-Hodgkin lymphoma (NHL)
    - and DLBCL, 157
    - familial aggregations,
      - hematolymphoproliferative cancers, 156
    - familial clustering, 156–157
    - follicular lymphoma, 157
    - fourfold excess, leukemia and lymphomas, 156
    - heterogeneous group, disorders, 156
    - primary immunodeficiency syndromes, 156
    - SEER population and SIRs, 157
    - Swedish Family-Cancer Database, 157
  - Noonan syndrome (NS)
    - characterization, 297
    - LEOPARD syndrome, 297
    - MAPK signal transduction, 298
    - subtypes, leukemia, 150, 151
  - Norris, W., 180
- O**
- OCCR. *See* Ovarian cancer cluster region (OCCR)
  - Ocular choristoma, 20
  - Ollier disease, 169
  - Optic gliomas, 19
  - Organ system neoplasms, 361–377
  - OSLAM syndrome, 168
  - Osteosarcomas
    - children, 167
    - chondrosarcoma, 169–170
    - contiguous gene syndrome, 169
    - Ewing sarcoma, 170
    - exostoses-anetoderma-brachydactyly type E, 169
    - familial osteosarcoma, 167
    - germline mutations, retinoblastoma gene, 168
    - hereditary multiple exostoses, 168–169
    - Langer-Giedion syndrome, 169
    - malignant degeneration risk, 168
    - mutations, *RECQL4*, 168
    - OSLAM syndrome, 168
    - osteochondromas, 169
    - rhabdoid tumors, 172
    - rhabdomyosarcoma, 170–171
    - sacroccygeal teratoma, 172–173
    - sarcoma-prone families, 167–168
    - truncating mutations, 169

- Ostergaard, P., 377
- Ovarian cancer
- carcinoma (*see* Carcinomas)
  - germ, epithelial/granulosa/theca cells, 105
  - neoplasms, 112
- Ovarian cancer cluster region (OCCR)
- multiple-case ovarian cancer families, 108
  - odds ratio, 108
- Ovarian neoplasms
- BRCA2* carrier, 112
  - gonadoblastoma, 112
  - Peutz–Jeghers syndrome, 112
  - SLCTs, 112
- P**
- Pachyonychia congenita (PC)
- blistering, 203–204
  - chronic ulceration/bullous formation, 204
  - germline mutations, *K17* gene, 204
  - nail abnormalities, 203
  - steatocystoma multiplex, 204
  - types, 204
- Palmar keratoses, 204
- Pancreatic cancer
- ataxia telangiectasia, 58
  - autosomal recessive inheritance, 57
  - BRCA2* mutations, 58
  - CDKN2A* mutations, chromosome 9p21, 57–58
  - familial clustering, 57
  - Fanconi anemia genes, 58
  - hereditary pancreatic carcinoma, 58
  - KRAS* mutations, 59
  - in males, 57
  - next-generation sequencing, 60
  - occurrence, 57
  - risk, adenocarcinoma, 59
  - screening, 59
  - Williams syndrome, 59
- Pancreatic endocrine tumors, 41
- Papillary thyroid carcinoma (PTC)
- DICER1* germline mutations, 32
  - familial, 31, 32
  - FAP-related cmv-PTC, 31–32
  - genetic susceptibility, 31
  - germline *SDHB/SDHD* variants, 32
  - somatic *BRAF* mutations, 32
  - sporadic, 31–32
- Parathyroid tumors
- genetic differential diagnosis, 34
  - germline mutations, 34
  - germline *RET* C634R, 35
  - management, 35
  - neoplasias, 34
  - somatic loss of heterozygosity (LOH), 35
- PARPi. *See* PARP inhibitors (PARPi)
- PARP inhibitors (PARPi)
- BRCA1/BRCA2* mutations, 95
  - PIK3CA inhibitors, 95
- PC. *See* Pachyonychia congenita (PC)
- Pelletier, J., 139
- Perlman syndrome, 298
- Peutz–Jeghers syndrome (PJS)
- clinical features, 299–300
  - description, 299
  - genetics, 300–301
  - medical management, 301
- Pheochromocytoma. *See* Adrenal gland tumors
- Pilomatrixoma, 204
- Pineal tumors, 8
- Pituitary tumors
- adenomas, 35
  - chromosome 11 allele loss, 35
  - growth-hormone-secreting, 35–36
  - McCune–Albright syndrome, 36
  - MEN 1, prolactinoma, 35
- PJS. *See* Peutz–Jeghers syndrome (PJS)
- Pleuropulmonary blastoma (PPB), 301–302
- PNETs. *See* Primitive neuroectodermal tumors (PNETs)
- POFD. *See* Polyostotic fibrous dysplasia (POFD)
- Polycythemia, 152–153
- Polyostotic fibrous dysplasia (POFD), 275–276
- Porokeratosis of mibelli, 198
- Porphyria
- HCV infection, 302–303
  - inborn errors, 302
- Pottern, L.M., 156
- PPB. *See* Pleuropulmonary blastoma (PPB)
- PPNAD. *See* Primary pigmented nodular adrenocortical disease (PPNAD)
- Prader–Willi syndrome, 148
- Primary immunodeficiency syndromes, 156
- Primary pigmented nodular adrenocortical disease (PPNAD)
- ACTH-independent Cushing’s syndrome, 203
  - defined, 39
  - germline *PDE11A* variation, 229
- Primitive neuroectodermal tumors (PNETs), 8–9
- Prostate cancer



- age and family history, 116
- BRCA2* mutations, 116
- cumulative risks, ethnicity, 115
- etiology, 115
- family linkage studies, 115
- genome-wide association studies, 117
- hereditary, 117
- HOXB13* G84E, 117
- IMPACT, 117
- Kaplan–Meier analysis, 116
- male *BRCA1/BRCA2* mutation carriers, 116
- risks, first-degree relatives, 115
- RR, 115
- Proteus syndrome
  - accelerated growth, 199
  - bony and adipose overgrowth, 199
  - dermatological, 199
  - mutations, *PTEN*, 199
  - somatic mosaicism, 199
- PTC. *See* Papillary thyroid carcinoma (PTC)
- Pulst, S.M., 6

## R

- Rahman, N., 139
- Rapp–Hodgkin syndrome, 195
- Rawstron, A.C., 150
- RCC. *See* Renal cell carcinoma (RCC)
- Renal cell carcinoma (RCC)
  - adult translocation carriers, 141
  - Birt–Hogg–Dube syndrome, 140
  - characterization, 140
  - clinical and molecular genetic evidence, 141
  - Cowden syndrome, 141
  - familial cases, 140
  - familial non-VHL clear cell, 141
  - and *FHIT*, 141
  - genes, 141
  - hyperparathyroidism–jaw tumor syndrome, 141
  - kindred, 140–141
  - in VHL, 140, 316
- Renal neoplasms
  - cystic nephroma, 139
  - DICER1* mutations, 139
  - FWT1*, 139
  - RCC, 140–141
  - ultrasound scans, 139–140
  - WAGR syndrome, 138–140
  - Wilms tumor, 137–138
  - WT1* and *WT2*, 139

## Reproductive system

- breast cancer (*see* Breast cancer)
- cervix cancer (*see* Cervix cancer)
- epididymal tumors, 121
- external genitalia, 114
- ovarian cancer (*see* Ovarian cancer)
- prostate cancer, 115–117
- testicular neoplasms, 117–119
- testicular tumors, intersex states, 119–121
- uterine tumors (*see* Uterine tumors)
- vaginal carcinoma, 114–115

## Retinal astrocytic hamartoma, 19

## Retinoblastoma

- benign retinal lesions, 16
- DNA techniques, 18–19
- germline mutation, 18
- identification, 17
- leukocoria, 15
- molecular genetic diagnosis, 18
- mutation detection, 17–18
- osteosarcoma, 17
- predisposition, 15
- RB1* gene, 17
- risk, 16
- second primary neoplasms and tumors, 17
- soft tissue sarcomas, 17
- survival rates, 15

## Rhabdoid tumors

- and MRT, 172
- SMARCB1* gene, 172

## Rhabdomyosarcoma

- classification, 171
- embryonal, 171
- germline mutations in *TP53*, 170
- segregation analysis, 171
- soft tissue, 171
- sporadic, 171

## Rombo syndrome, 189

## Rothmund–Thomson syndrome, 304

## S

## Sacroccygeal teratoma

- adult testicular gonadal germ cell tumors, 172–173
- Currarino triad, 173
- sickle-shaped sacrum, 173

## Salivary gland tumors

- cancer incidence, 47
- familial occurrence, 47
- germline mutations, *CYLD1* gene, 48
- MALT lymphomas, 48
- populations, 47
- single two-generation Inuit family, 47

- Salmonsén, P.C., 18
- Sapienza, C., 16
- Sarcomas
- children with soft tissue, 171
  - extraskelatal myxoid chondrosarcomas, 172
  - KS, 172
  - osteogenic (*see* Osteosarcomas)
  - synovial, 171
  - uterine leiomyomas, 172
- SCC. *See* Squamous cell carcinoma (SCC)
- Schlemper, R.J., 153
- Schwartz, A.G., 27
- SCID. *See* Severe combined immunodeficiency disease (SCID)
- Sclerocytopsis, 199
- Scott, R.H., 140, 255
- Sellers, T.A., 27
- Sertoli–Leydig cell tumors (SLCTs)
- androgenization, 112
  - STK11 mutation carriers, 112
- Severe combined immunodeficiency disease (SCID), 305
- Shugart, Y.Y., 155
- Shwachman–Diamond syndrome
- description, 305
  - diagnostic criteria, 305, 306
  - genotype analysis, 305
- Simpson–Golabi–Behmel syndrome, 306
- SIRs. *See* Standardized incidence ratios (SIRs)
- Skin cancers
- Bazex syndrome, 187–188
  - BCC, 185–187
  - dermatological malignancy (*see* Dermatological malignancy)
  - description, 178
  - EV, 190
  - familial (*see* Familial melanoma)
  - Ferguson-Smith-type self-healing epithelioma, 190–191
  - genetic predisposition, melanoma (*see* Melanoma)
  - giant congenital melanocytic nevus, 185
  - Rombo syndrome, 189
  - SCC, 189–190
- SLCTs. *See* Sertoli–Leydig cell tumors (SLCTs)
- Small intestine tumors
- adenocarcinoma, small bowel, 60–61
  - age factor, 60
  - celiac disease, 61
  - Crohn's disease, 61
  - familial polyposis, 61
  - leiomyomas and lipomas, 60
  - pancreatoduodenal endocrine, 61
  - stage I–III disease, 60
  - upper gastrointestinal surveillance, 61
- Smith, M.J., 6
- Smith, O.P., 305
- Sorensen, S.A., 289
- Sotos syndrome, 306
- sPNETs. *See* Supratentorial PNETs (sPNETs)
- Squamous cell carcinoma (SCC)
- albino, 189
  - azathioprine and leukoplakia, 189
  - epidermal keratinocytes, 189
  - genetic disorders, 189
  - hereditary skin disorders, 189
  - light-skinned people, 189
- Standardized incidence ratios (SIRs), 157
- Steatocystoma multiplex, 200
- Stillier, C.A., 290
- St John, D.V.B., 64
- Strong, L.C., 7
- Supratentorial PNETs (sPNETs), 9
- Synovial sarcomas, 171
- Syringomas
- autosomal dominant condition, 199
  - multiple cylindromatosis, 197
  - and trichoepitheliomas, 192
- T**
- Taylor, M.D., 8–9
- Testa, J.R., 28
- Testicular neoplasms
- chromosomal analysis, 119
  - cryptorchidism, 118, 119
  - familial risks, 118, 119
  - “gr/gr” deletion, 119
  - heterogeneous and X-linked locus, 118
  - Klinefelter syndrome, 118
  - malignancy in males, 117
  - Sertoli cell tumors, 118–119
- Testicular tumors, intersex states
- chromosomal mosaicisms, 119–120
  - gonadoblastoma, 119
  - Klinefelter/XXY syndromes, 120
  - Müllerian duct and pseudovaginal perineoscrotal hypoplasia, 120–121
  - single gene defect, 120
  - Y-chromosomes, 120
- Thomas, L.B., 142
- Thrombocythemia
- activating mutations in *MPL* gene, 153
  - bleeding and thrombotic events, 153

- familial cases, 153
  - MPL mutations, 153
  - myeloproliferative disorder
    - characterization, 153
  - polycythemia rubra vera, 152–153
  - somatic mutations, 153
  - trisomy 8 and 9, del(13q) and dupl(1q), 153
- Thuwe, I., 4
- Thymomas, 26
- Thyroid tumors
  - benign neoplasia, 34
  - description, 31
  - FTC, 33
  - MTC, 33–34
  - PTC, 31–32
- TMD. *See* Transient myeloproliferative disorder (TMD)
- Transient myeloproliferative disorder (TMD), 151
- Trichoepithelioma, 200
- TS. *See* Turner syndrome (TS)
- Tuberose sclerosis
  - bones and cardiac, 309
  - diagnostic criteria, 309–310
  - eyes, 308
  - locus heterogeneity, 309
  - lungs, 309
  - mutation rate, 307
  - skin, 307
  - teeth and kidney, 308–309
  - TSC2 and APKD1 genes, 308–309
- Turcot syndrome, 311–312
- Turner syndrome (TS), 312
- Tylosis, 200
- U**
- Umar, A., 259
- Ureter and renal pelvis cancer
  - carcinoma, 141
  - HNPCC syndrome, 142
  - medullary carcinomas, 142
- Urinary system
  - bladder cancer, 142–143
  - renal neoplasms (*see* Renal neoplasms)
  - ureter and renal pelvis, 141–142
- Uterine leiomyomas, 172
- Uterine tumors
  - carcinoma (*see* Carcinomas)
  - choriocarcinoma, 104
  - description, 101
  - fallopian tube carcinoma, 104–105
  - leiomyoma, 101–102
  - ovarian (*see* Ovarian cancer)
- Uveal melanoma, 21–22
- V**
- Vaginal carcinoma
  - Brenner tumors and leiomyomas, 114–115
  - Ewing sarcoma and peripheral neuroectodermal tumor, 115
  - giant hypertrophy, labia minora, 115
  - invasive epithelial and *in situ*, 114
- Valverde, P., 179
- van Dijken, P.J., 153
- Vasen, H.F., 258
- Vestibular schwannoma, 2
- VHL. *See* von Hippel–Lindau (VHL) disease
- Vieregge, P., 3
- von Hippel–Lindau (VHL) disease
  - brain stem hemangioblastoma, 314–315
  - cerebellar hemangioblastoma, 314
  - description, 313
  - diagnostic criteria, 313–314
  - ELSTs, 317
  - hemangioblastoma, 20–21
  - molecular genetics, 317
  - pancreas, 317
  - pheochromocytoma, 316–317
  - polycythemia, 152–153
  - RCC, 316
  - retinal angiomas, 315
  - spinal cord hemangioblastoma, 314
- W**
- Waldenstrom macroglobulinemia, 158
- WAS. *See* Wiskott–Aldrich syndrome (WAS)
- Webster, A., 21
- Werner syndrome (WS)
  - clinical diagnosis, 318
  - description, 318
  - LMNA gene, 318
- Wiedemann, H.-R., 224
- Wiernik, P.H., 157
- Wiestler, O.D., 20–21
- Wiley, J.S., 150
- Wilms tumor
  - description, 137
  - median age at diagnosis, 137
  - mesenchymal renal stem cell/metanephric blastema, 138
  - nephrogenic rests, 138
  - and sporadic aniridia, 137

Wilms tumor–aniridia–genital abnormality–  
mental retardation (WAGR)  
syndrome

definition, 132

Denys–Drash syndrome, 139

non-WAGR children, 139

PAX6 and WT1, 138

Wiskott–Aldrich syndrome (WAS)

ataxia telangiectasia, 156

lymphoproliferative disorders, 155

XLN and XLT, 319–320

WS. *See* Werner syndrome (WS)

## X

Xeroderma pigmentosum (XP)

autosomal recessive disorders, 320–321

classification, 321

De Sanctis–Cacchione syndrome, 321

mutations, genes, 321

prenatal diagnosis, 322

UVA sensitivity, 322

X-linked lymphoproliferative disorder, 320

XP. *See* Xeroderma pigmentosum (XP)

## Y

Y-chromosomes

germ cell tumors, 119–120

gonadoblastoma, 120

“gr/gr” deletion, 119

## Z

Zollinger–Ellison syndrome

clinical diagnosis, MEN 1, 280

gastrinomas, 278