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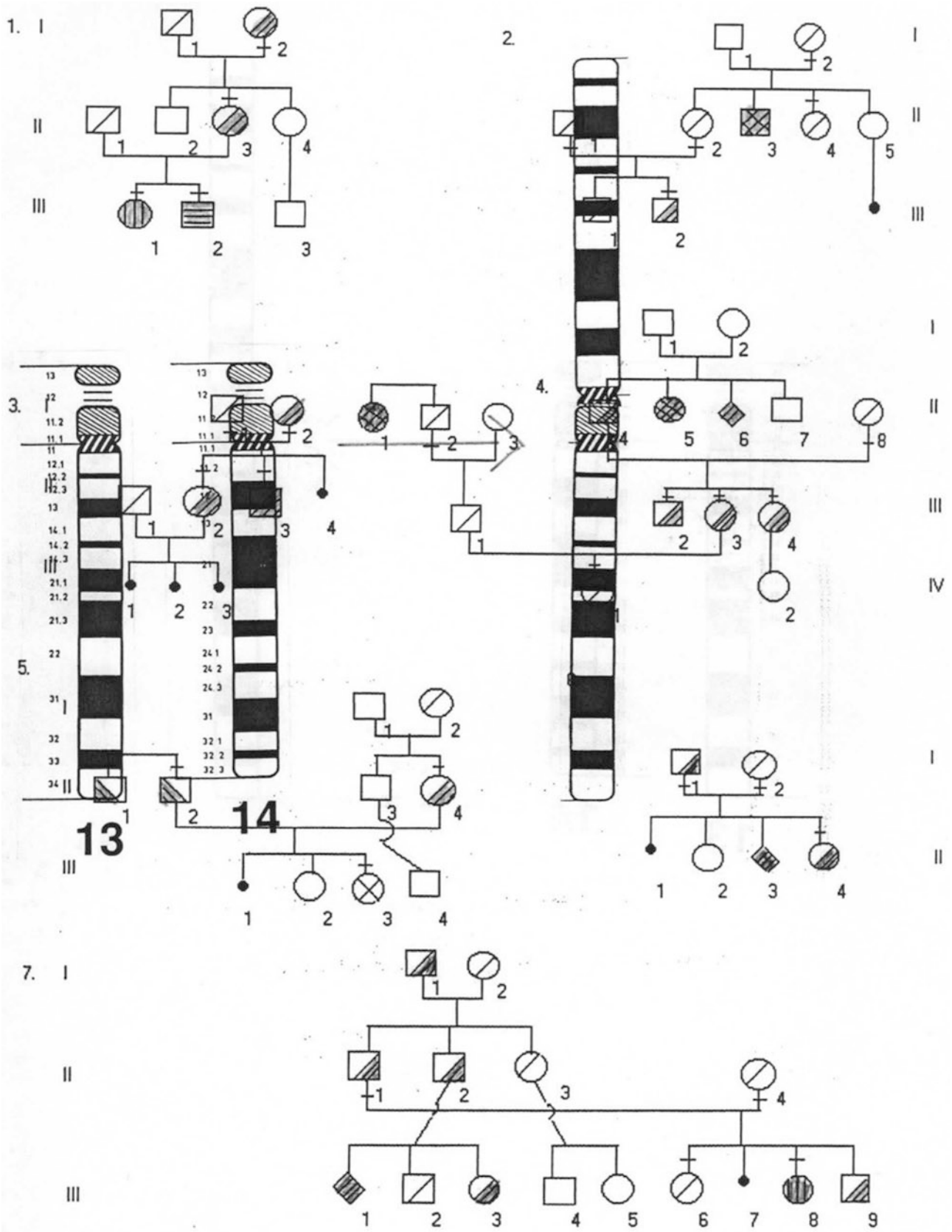
Human Chromosome Atlas

Introduction to Diagnostics of Structural Aberrations

Springer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Introduction to Diagnostics of Structural Aberrations

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Preface

Cytogenetics is a relevant field of research in Genetics and especially in Human Genetics. Over the past 57 years it has developed explosively and at the same time it was divided into different research and application areas, the most relevant of them were theoretical Cytogenetics as a basic science, Tumor Cytogenetics, investigations on Mutagenesis research on Evolution, and Population Cytogenetics. Parallel with the development of these special fields of research, cytogeneticists established a close cooperation to related fields of research such as Molecular Genetics, Clinical Genetics, Cell Biology, Biology of Reproduction, Oncology or Pathology.

Progresses in the subject have always been combined to progresses in investigation methods. The latter ones usually lead to new main topics of research and to improved possibilities of diagnoses when investigating patients being carriers of chromosome abnormalities. From the beginning, Cytogenetics was characterised by an intensive international cooperation, which lead among others to common decisions in questions of chromosome nomenclature (ISCN). Specific symposia, workshops, seminars, and continuing education organisations on national and international basis lead to close personal contact between scientists and research groups, to counseling of young scientists and as impetus for many future-oriented projects.

It is desirable that this inspiring atmosphere is accompanying cytogenetic scientists in future as in the past.

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Contents

Introduction

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The present atlas of structural chromosome aberrations is intended as a diagnostic aid in applied Cytogenetics, when analysing the human karyotype. It demonstrates the spectrum of the different types of chromosome abnormalities by a combination of karyogram and ideogram, it compares the expressiveness of different banding techniques, and it gives the karyotype formula and describes morphological peculiarities of each presented case. Furthermore, it shows potential problems in detecting aberrations and mentions necessary additional investigations and peculiarities, which have to be taken into account when counseling carriers of a chromosome aberration or their relatives.

The second part of the atlas contains a detailed description of variants of non-coding DNA and its relevance when analysing chromosomal peculiarities. Based on our own experiences, it seemed necessary to characterise mutations in these defined chromosome regions in detail, to give an overview on the relevant staining techniques when analysing these segments and to give data on the frequencies and localisations of mutations. It will be explained—based on the examples given here—how difficult it can be to differ between mutations in polymorphic heterochromatic regions which are of no genetic relevance and relevant genetic mutations in euchromatin, because the morphology is often similar.

It is our intention to present a broad spectrum of chromosome abnormalities. We are not claiming to give a complete collection of all possible aberration types, but we wish to give an impression on the spectrum of findings of an institute of applied Cytogenetics and Clinical Genetics.

Certainly, many of the users of this atlas analysed themselves other, most relevant cases of aberrations or developed new strategies when investigating problematic cases. We would be glad, if the colleagues will come in contact with us.

To all colleagues working in the field of Cytogenetics, we wish for the successful future and satisfying research projects and we would be glad if the chromosome atlas presented here will be of help to them.

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Structural Chromosome Aberrations

2

Structural chromosome aberrations or chromosome mutations represent apart from aneuploidies the most frequent pathologic findings in applied chromosome diagnostics. But they also occur as combinations of both types as in unstable rearrangements or in chaotic karyotypes of early stages of embryonic development.

Depending on the indication for chromosome analysis—child with developmental retardation, spontaneous abortions, sterility—the majority of aberrant karyotypes will be unbalanced or balanced. Furthermore, it could be shown that the frequency of de novo and familial aberrations is depending on the type of the aberration. Chromosome mutations are divided into intrachromosomal and interchromosomal aberrations. In addition, complex chromosome rearrangements (CCR) represent a special group of abnormalities, where intrachromosomal and interchromosomal aberrations can be combined in one genome. Their investigation affords the combination of chromosome analyses, microarray and FISH and their characterisation is still under development.

In the following intrachromosomal aberrations are shown first, followed by the interchromosomal aberrations.

2.1 Intrachromosomal Rearrangements

The following types of aberrations are included in this group:

Deletions, duplications, inversions (para- and pericentric), ring chromosomes, isochromosomes.

2.1.1 Inversions

This chromosome atlas is based on pathologic chromosome findings, collected at our institute in Düsseldorf. As the main focus of our institute is on the investigation of infertile couples before ICSI therapy, the majority of pathologic findings are balanced rearrangements in the group of inversions (60%). As they extremely well represent the spectrum of intrachromosomal rearrangements, the methodological requirements, and the order of genetic counseling of the carrier of an inversion, this group will be represented in detail in the following chapter. Particularly it will be pointed out, in which cases molecular-cytogenetic and molecular genetic investigations (FISH), microarray are additionally required. However, it should be understood that, if a balanced chromosome rearrangement has to be expected in the patient, chromosome analyses remain the most relevant investigation.

2.1.1.1 Pericentric Inversions

This type of aberration is characterised by the position of the centromere within the inverted region. If the two breakpoints in the short (p) and long (q) arm show different distances to the centromere, the centromere index will be changed. The recombination frequency in meiosis will depend on the chromosome involved and the length of the inverted region. Very small inversions can be inherited over a number of generations exclusively in the balanced condition. Caused by an abnormal course of meiosis carrier of balanced inversions have an increased risk of the development of uniparental disomy (UPD) in the offspring. Inversions of the X-chromosome often lead, in contrast to inversions of the autosomes, to the development of gene-function irregularities.

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2.1.1.2 Paracentric Inversions

This type of inversion is characterised by the position of both breakpoints in the same chromosome arm (p or q), the centromere index has not changed, and the diagnosis is only possible by the altered banding pattern in the inverted region. A high structure resolution of the chromosomes is required (at least 550 bands per genome) for a reliable diagnosis. That is why paracentric inversions were only rarely diagnosed in the first decades of cytogenetic investigations. Nowadays it is well known that paracentric inversions represent a frequent type of aberrations.

When analysing this type of abnormalities it always has to be kept in mind that they must be differentiated from insertions by FISH, as the latter group is characterised by a high genetic risk whereas that of paracentric inversions can usually be considered as low (about 1‰).

Paracentric inversions of the X-chromosome are rare aberrations, special breakpoints in the long arm can lead to gonadal dysfunction.

2.1.2 Deletions

Deletions are also defined as partial monosomy. In a wider sense ring chromosomes can be attributed to this group. But in the presentation given here they were described in a chapter of their own as their morphologic peculiarities and the often observed secondary changes make it practical. The size of the deleted regions shows high variability from a length of single base pairs (detectable by molecular genetic methods), several kb up to 5 Mb (analysable by specific FISH probes in cases suspicious for micro-deletion, or by molecular techniques) and finally deletions of 5 to more than 20 Mb, diagnosed by chromosome analyses. Only the latter group will be described here in detail.

This type of aberration is further subdivided in terminal deletions, which are caused by only one chromosome break and interstitial deletions which are caused by two breaks, followed by the reunion of the breakpoints.

Deletions occur in short (p) as well as in the long (q) arm of a chromosome and they have been observed for all human chromosomes. Large deletions are rare. The interchromosomal distribution of deletions shows differential frequencies, of which the most frequent ones represent well defined chromosome syndromes (i.e. 4p-, 5p-, 18p-, 18q-). Deletions have already been diagnosed and described in detail in the prebanding area (i.e. Cri-du-chat syndrome, de Grouchy syndrome I and II). Recent investigations have shown that terminal deletions usually have a telomere, which stabilises the end of the chromosome. Terminal deletions are about 7-times as frequent as interstitial ones. Only part of deletions has originated in the carrier de novo, others are the unbalanced inherited form of a parental translocation. Regarding the deletions 4p and 5p the percentage of inherited aberrations amounts to 8–15%. Therefore, when a deletion is analysed in a patient this always leads to the indication for chromosome investigation in the parents. In the detection of translocations by additional analyses it is notable that the second chromosome is not randomly distributed in the genome, but there are preferred combinations.

More than 80% of deletions have been originated de novo in the carrier, the majority of them in the paternal meiosis. In single cases, if the retardation of the carrier is only marginal, the deletion can be inherited to an offspring.

2.1.3 Duplications

Chromosome duplications are also defined as partial trisomies. The duplicated segments originate from replication errors within one chromatid, by an unequal exchange between sister chromatids or by translocation between homolog chromosomes. Often duplications are combined with deletions. The phenotypic changes of a patient with segmental duplication are usually less serious than a deletion of the same region. In some cases duplications and deletions of same chromosome region are characterised as “type” and “counter-type” (i.e. 4p, 9p, 22q11.2).

Duplications are subdivided in tandem arrangements of the aberrant region and in inversion duplications. In single cases even triplications of chromosome segments have been described, and in these patients the gene-dosis-effect was significantly elevated.

Depending on the mode of development the origin of duplications can be uniparental or biparental. They can be the result of a meiotic or postzygotic error, in the latter case the carrier will show the aberration as a mosaic. Special forms of duplication are the supernumerary marker chromosomes and isochromosomes. The great majority of duplications has originated de novo in the carrier. When estimating the recurrence risk in the course of genetic counseling the possibility of a gonadal mosaic in one of the parents has to be taken into account. Single cases of familial duplications have been reported,

but in these cases the carrier parent showed only minor phenotypic changes. Microarray investigations during the last years lead to a significant increase of well-defined microduplication syndromes.

2.1.4 Ring Chromosomes

Three different types of ring formation have been observed:

1. The fusion of two breakpoints in one or two euchromatic regions and loss of the acentric fragments in the short and/or the long arm (p, q).
2. The fusion of the two telomeres without loss of euchromatic segments. But it leads to mitotic abnormalities and frequent losses of the ring.
3. A fission in the centromere is followed by a U-type exchange.

The frequency of ring chromosomes is estimated to range from 1:28 to 1:62,000, with chromosomes 13 and 18 being most frequently involved. Familial cases are, as expected, extremely rare (about 1%) and they are only observed in ring chromosomes 21 and 22. The majority of rings are of paternal origin. The phenotype of the patients is very variable caused by the different break points leading to a different size and thus gene content of the deleted regions. Caused by irregularities in the S-phase of the cell cycle partial duplications can originate.

Ring chromosomes are often difficult to analyse:

1. Very small rings are not easy to distinguish from derivative chromosomes.
2. If the ring is balanced or the deleted region is only submicroscopic in size (less than 5 Mb) the indication for chromosome investigation may not be given.
3. If the ring is restricted to one germ layer or even one tissue, the cell system analysed may not contain the ring.
4. In cases of low grade mosaicism it can be difficult to find mitoses with the ring chromosome.

Often a karyotype with a ring presents as “dynamic mosaic”. In these cases, especially if the ring has two centromeres, it is unstable in the course of the cell cycle and new cell lines develop continuously. Therefore after prenatal diagnosis of an unstable ring it will be impossible to predict the phenotype of the child. Ring chromosomes are observed in cases with a normal chromosome number and as additional structures. The microscopic analysis of rings is not always easy, as they have a three-dimensional structure and therefore they appear different in view depending which angle you look it from.

In the investigation group represented here patients with ring chromosomes were diagonally in a few cases as the majority of them was analysed because of fertility problems and was phenotypically without peculiarities (investigations before ICSI-therapy).

2.1.5 Isochromosomes

After a transverse separation of a centromere, i.e. chromosome fission, both arms (p and q) can be duplicated. The result will be two isochromosomes, one of the short and one of the long arm. The karyotype of the proband can be balanced, in case the second normal homolog chromosome is lost by the so called aneuploidy rescue. Carrier of this particular rearrangement cannot have healthy offsprings.

The more frequent type of isochromosome formation starts by an unequal centromere fission resulting in one arm containing the whole centromere and the second being acentric. The acentric arm gets lost and the result is the development of an isochromosome in a karyotype with normal chromosome number but deletion of one and duplication of the other chromosome arm. A frequent example of this type of aberration is the isochromosome Xq. Besides this type of aberration isochromosomes can also be observed as additional derivates. In these cases the karyotype is tetrasomic for the aberrant chromosome arm, as in isochromosome 12p, the Pallister Killian syndrome. Furthermore by inversion-duplication a dicentric isochromosome can develop, which is often unstable in the course of mitoses caused by an incomplete inactivation of the second centromere which in the course of the somatic cell divisions frequently gets lost and leads to monosomy of the chromosome involved. This type of secondary aberration is more often observed in gonosomes than in autosomes, leading to mosaic formation with a X0 cell line. These observations lead to the conclusion, that in all cases of dicentric

isochromosomes the possibility of a mosaic formation has to be considered and thus the number of mitoses analysed has to be at least 30–50.

The majority of isochromosomes develops during meiosis. But they can also result from postzygotic cell divisions and then present as mosaic. If such a mosaic is restricted to the gonads of a healthy proband, the aberration can appear as an aberration in all cells in the offspring.

2.2 Interchromosomal Rearrangements

Interchromosomal caused changes of chromosome structure are a heterogenous group of aberrations. The exchanges of segments afford at least 2 break points, but it can be also up to 7. The size of the rearranged chromosome regions differs between 5 and more than 50 Mb. Interchromosomal rearrangements can be caused de novo in the carrier or they are of familial origin. In one individuum different types of aberration can be combined. The interchromosomal aberrations are categorized in 4 main groups, of which the translocations are further subdivided in 2 subtypes. The main groups are translocations with the 2 subgroups reciprocal and Robertsonian translocations, complex chromosome rearrangements (CCR), insertions and part of marker chromosomes.

2.2.1 Translocations

The majority of translocations concern rearrangements between heterologous chromosomes, only a few occur between homologous, and they represent a very variform type of aberrations. Most of the cases of heterologous exchanges take place between 2 chromosomes. The breakpoints can be localised both in heterochromatic regions, both in the euchromatin or in the combination of hetero- and euchromatic segments. In cases, when one of the translocation products is significantly reduced in size in comparison to the original chromosome and therefore has left only small regions in common with that one, the course of meiosis is often pathologic and leads to mistakes in its distribution and as a consequence to an increased genetic risk.

The majority of translocation chromosomes are stable in their structure, but instable rearrangements do exist and they are defined as “jumping translocations”. Translocations present with a varying genetic risk of the carrier, reaching from less than 1% up to 100% in cases of homologous translocations. At the same time the group of carriers of translocations of the homologs gives us the possibility to define the frequency of de novo mutations in this type of aberrations.

2.2.1.1 Reciprocal Translocations

Exchanges of segments between chromosomes are a frequent type of structural chromosome aberration and they are among others characterised by specific “hotspots” of the break points. Additional investigations by FISH methods increase the amount of reciprocal translocations significantly and the localisation of the breakpoints becomes more precise. The distribution pattern of the aberrations reveals significant differences when the investigation group consists of probands from the general population or by selection of carriers with phenotypic abnormalities.

A special group of aberrations are exchanges between an autosome and a gonosome, as in these cases additional risk factors exist in carriers of the balanced rearrangement caused by pairing abnormalities in meiosis and an abnormal X-inactivation pattern in females. More than 95% of reciprocal translocations occur between 2 heterologous chromosomes. The genetic risk of a carrier of the balanced translocation depends on the size and the gene content of the segments exchanged. In the majority of cases the unbalanced karyotype reveals the combination of a partial duplication and deletion. Additionally, unbalances caused by an unequal crossing over in the breakpoint regions during meiosis are observed. Furthermore there exists a risk factor caused by malsegregation of the smaller translocation chromosome during meiosis. A main risk factor stated in the course of genetic counseling of a carrier and/or his relatives is the probability for birth of a handicapped child, but additionally the increased risk of spontaneous abortion and still birth as well reduced fertility of the translocation carrier have to be taken into account. Depending on the type of translocation these 3 risk factors can be reduced to one, either if all forms of unbalanced karyotype are lethal (i.e. whole arm translocations), then only the fertility is reduced in the carrier. The second possibility is realised when the unbalanced karyotype permits only the first steps of ontogenetic development, then the conceptus dies off and leads to a spontaneous abortion, but handicapped children are never born.

When the carrier of an unbalanced translocation is viable, usually also an increased risk of spontaneous abortion is given for the balanced parent and besides his fertility is reduced.

The risk for the birth of children with unbalanced karyotype and for an increased rate of abortions is statistically double in females compared to men (20:10%). This is caused by a strong selection against unbalanced karyotypes in spermatogenesis. Depending on the different types of translocation it varies from less than 1% to almost 50%. Therefore it is most important in cases of familial translocations to perform additional investigations in the relatives, to get more precise informations on the specific translocation in the family coming for genetic counseling as to the number of healthy children, pathologic pregnancies and the inability to have children of the further translocation carriers in the family.

Epidemiologic investigations showed that reciprocal translocations have a frequency of about 1:500 in the general population. They occur de novo and familial, and in the latter group it has been possible to trace back single translocations over a period of more than 300 years.

2.2.1.2 Robertsonian Translocations or Centric Fusions

Robertsonian translocations are also classified as whole arm translocations. This group comprises the most frequent structural chromosome aberrations with an incidence of 1 in 1000 newborns. Involved in this type of rearrangement are the acrocentric chromosomes, i.e. 13, 14, 15, 21, 22. The most frequently observed breakpoint is p11.2. The chromosome fusion takes place between homologous and heterologous chromosomes.

The original assumption that fusions of the nucleoli or tight associations of NOR-regions play a role in the origin of Robertsonian translocations could not be confirmed by more extended investigations. In heterologous fusions the two translocation chromosomes are usually derived from one parent, and about 90% of them develop during maternal meiosis I. The breakpoints in the combinations 13/14 and 14/21 are practically always the same caused by inverted homologous sequences in p11.2. All other combinations show a significant variation as to their breakpoints. In meiosis I trivalents are formed by pairing of two normal homologous and the translocation chromosome. By an abnormal course during the further phases of meiosis up to 7 different types of gametes can originate. The two most frequent heterologous fusions are 13/14 and 14/21 with 30% each. All fusions of homologous chromosomes occur in a frequency between 0.5 and 3%. Zygotic and postzygotic fusions seem to be rare events. They can be delineated when biparental in origin.

The frequency of fertilisation is not reduced in Robertsonian translocations, but a selection against conceptus with unbalanced karyotype occurs in the postzygotic period.

Uniparental disomy (UPD) can develop by trisomy or monosomy rescue, but its frequency is estimated to be less than 0.5%. If chromosomes 14 or 15 are involved, UPD leads to characteristic malformation syndromes, such as Prader Willi or Angelman syndrome. Male carriers of Robertsonian translocations have a risk of infertility which is about 7-fold increased compared to the general population. The karyotype of the conceptus after PID was pathologic in 90% of the cases and even chaotic in 60%. One cause of these abnormalities is suspected in an abnormal course of meiosis I: the short arms (p) of the acrocentrics remain unpaired during the formation of a triradial and in the next phase they pair with the X/Y bivalent which then leads to a fragmentation of the nucleus in the following late prophase of meiosis I. But this pathologic course is not obligatory and a large intrafamilial variation of this effect has been observed.

The carrier of a balanced Robertsonian translocation usually has 45 chromosomes, because the heterochromatic short arms without a centromere get lost, while the carrier of the unbalanced karyotype has 46 chromosomes in the majority of cases, in rare cases it can be 47 chromosomes. If the balanced carrier is offspring of two related parents, each of them carrying the same chromosome fusion, he can have the translocation twice and his karyotype comprises 44 chromosomes. In cases when both products of a Robertsonian translocation receive a centromere, the heterochromatic short arm regions occur supernumerary in the karyotype. These heterochromatic derivates of the short arms can insert euchromatic segments by unequal crossing over in the meiosis I and are then inherited to the offspring as chromosome aberrations leading to phenotypic abnormalities in the carrier.

2.2.2 Insertions

Insertions are defined as complex chromosome rearrangements, which afford three breaks for their formation, two of them to cut the segment from the donor and one for insertion in the recipient chromosome. The frequency of insertions in life born children is 1:5000. Regarding the cases of *intrachromosomal* rearrangement the dislocation of the cut out segment occurs within the donor chromosome. In cases of paracentric insertion the centromeric index remains unchanged, but in pericentric insertions the segment is transferred to the other chromosome arm and then the centromere index changes.

After *interchromosomal* insertion the centromere index of donor and recipient changes. The final position of the fragment compared to its alignment in the donor chromosome and compared to the localisation of the centromere will be either direct or inverted (180°). The inserted segments are either built from euchromatin or heterochromatin and in the latter case a special group exists only of the NOR-region. The size of the inserted regions reaches from 5 to more than 10 Mb in cases which are analysable by microscope, but the majority of them are cryptic, i.e. less than 5 Mb and they often contain transposons.

During the meiosis, when the homologue chromosomes are pairing, an intrachromosomal, insertion often forms loops which can lead unequal recombination products with partial deletions and duplications. The theoretical risk for the formation of an unbalanced karyotype is about 50%, but depending on the size and the gene content of the segment the risk for the birth of a handicapped child is small. When the insertion segments are large they can form double loops and in the unbalanced karyotype of the offspring deletions can be combined with duplications. Interchromosomal insertions often develop during meiosis and give rise to four different types of gametes, two of them showing an unbalanced karyotype.

A special feature during the development of insertions is the formation of fragile sites in the chromosome, which lead to an increased tumor risk if the region contains tumor suppressor genes.

Insertions reveal an unequal intra- and inter-chromosomal frequency as to their distribution in the karyotype, frequent loci being 2q, 5q, 7q and 13q. The risk for the birth of a child with unbalanced karyotype, non-regarding size and gene content if one of the parents is balanced carrier amounts to 36% for the mother and 32% for the father. This risk amounts to 50% in certain types of insertion and thus it represents the highest genetic risk of chromosome rearrangements, apart from fusions of the homologous chromosomes.

Recent investigations lead to the observation that insertions can cause imprinting diseases.

2.2.3 Complex Chromosome Rearrangements (CCR)

Complex chromosome rearrangements can be restricted to only one chromosome but also three and more chromosomes can be involved. They are characterised by more than two breakpoints in one or more chromosomes. The types of rearrangement which lead to a CCR are translocations as the main group, besides inversions and insertions, and they can be combined with deletions and duplication when the karyotype is unbalanced.

A special type of CCRs is the combination of different independent rearrangements in one karyotype, as for example a reciprocal and a Robertsonian translocation or a translocation and an inversion.

CCRs can occur as balanced rearrangements. But the majority of them, when they are de novo aberrations in the carrier, are unbalanced and cause phenotypic abnormalities in the carrier such as mental retardation, which is diagnosed in 10–15% of them. When the CCR appears balanced additional molecular genetic investigation often reveal the presence of cryptic aberrations or gene disruptions. When estimating the genetic risk of the carrier presenting a CCR, it is necessary to take into account the chromosomes involved and the number and localisation of the break points, as these factors influence the course of meiosis by formation of different types of multivalents and therefore the frequency of unbalanced gametes. For example in a proband with a three chromosome rearrangement interphase FISH revealed 20 different karyotypes in the carrier, of which 18 were unbalanced. Additionally to the dominating structural aberrations meiotic non-disjunction can occur and lead to an aneuploidisation of the gametes.

It has been assumed that the development of a CCR can be caused by chromosome breaks which become unstable after an incomplete repair. Up till now more than 250 cases of CCR are known from the literature. Familial cases show that the majority of them are of maternal origin, as in the male carrier of a balanced CCR the abnormality often leads to a reduced fertility or even to sterility. In the majority of familial cases the number of breakpoints is less than in de novo cases, that means 4 and less.

The chromosomes involved in CCR formation show an unequal distribution in their frequency. The large chromosomes are more often involved than the small ones and chromosomes 3, 7, 1, 5, 8 and 6 are most frequently diagnosed in this type of aberration. Intrachromosomal analyses of the breakpoints revealed hot spots of aberration such as 4q28.3, 18q21.3, 18q11.2, 21q11.2 and 22q11.2. The position of the breakpoints is located in the euchromatin in 85%, in the centromere in 10%, and in 5% in the telomeric region. When analysing the position of the breakpoints in the chromosome 65% of them are located intermediate, 20% distal and 15% proximal.

2.2.4 Marker Chromosomes (Chromosome Derivates)

Marker chromosomes are a special group of chromosome derivates, which cannot be classified according the ISCN nomenclature, as they don't show normal banding pattern over a larger segment which enables their identification. They are diagnosed either in addition to the normal chromosomes—supernumerary marker chromosomes (SNMC), or as structurally abnormal chromosomes (ESAC)—or they are observed in a karyotype, with normal chromosome number. In cases of additional marker chromosomes only one is present in the majority of cases, but there are also cases published with two different or two times the same marker in the pathologic karyotype. Their frequency is about 1:1000 in the normal population and 3:1000 in probands with mental retardation.

In the majority of cases marker chromosomes are less in size than chromosome 21—the smallest human chromosome—and they contain increased amounts of heterochromatin. According to their structure, they are divided into three main groups: marker with satellites on both sides, on one side, and without satellites. Further characteristic features are the number of centromeres—mono- or dicentric—and the composition of only heterochromatic segments or the combination of euchromatic and heterochromatic regions. The majority of SMC are derivates of the acrocentrics (about 70%) of these nearly 40% are derived from chromosome 15. Maker chromosome occur de novo and familial. A peculiarity of the latter group is the frequent formation of mosaics (about 50%). In familial cases with a heterochromatic marker in a healthy carrier an increased genetic risk is given for his children by the possibility of the occurence of an unequal crossing over in meiosis with the normal original chromosome leading to the insertion of euchromatin into the marker which then causes malformations and/or retardation in the progeny. Marker chromosomes can be unstable in the course of postzygotic mitoses and thus decrease in frequency pre- and postnatal and these changes show a different speed of reduction in different cell systems such as lymphocytes or fibroblasts.

Mutations in Non-coding-DNA Regions

3

Synonyms: heteromorphisms, structural variants, polymorphisms.

For a long time the constitutive heterochromatin has been regarded as neglectable as to its significance of mutations in chromosome structure and function. Recent investigations made it obvious that it is relevant for the course of sex differentiation and mitoses. The different types of heterochromatin were characterised in detail which lead to the definition of subtypes and if the consequences of mutations in these regions were analysed in detail.

In the following sections 5 different types of heterochromatin and one of genetic non relevant euchromatin are presented in detail.

3.1 Euchromatic Variants

In this type of structural variants the recognition in most cases depends on size differences of one band, usually AT-rich, between the two homologous chromosomes of one pair. It originates either by duplication or by partial deletion of the region. If the genes located in these bands encode for quantitative features the changes can be compensated by other genes being connected in a network of comparable functions.

Up till now 17 different euchromatic variants have been characterised. The most frequent are 4p16, 8p23.1, 9p12, q12, 9q13, 15q11.2, 16p11.2. Further frequent variants have been analysed in the last years in the subtelomeric regions of 1q, 9p and Xp. Their number can be expected to increase with increasing investigations by microarray. If the healthy parents and their handicapped child present with the same euchromatic variant this can be caused by a number of facts:

- The gene presents with variable penetrance or reduced expression,
- in meiosis of the carrier parent unequal crossing over lead to partial duplication or deletion of relevant neighbouring genes,
- modificating genes play a role,
- by insertion of parts of the variable band into its sister chromatid a tolerable gene content is exceeded.

Therefore, genetic counseling is always difficult in prenatal cases. The type of aberration are deletions and duplications with a size of 3–30 Mb.

3.2 Satellites

They appear as stalked appendices of the short arms (p) of the acrocentric chromosomes. They consist of satellite DNA with a high number of repetitions. They are strongly contracted and therefore stain intensively after Giemsa-staining. Mutations in these regions affect their number, size and staining characters. The types of mutations are deletions (up to 4 of the 10 regions), duplications and translocations with non-acrocentric chromosomes. The most frequent translocation Y/15 is diagnosed in 1:3500 persons of the general population.

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Other rearrangements are jumping translocations and translocations of euchromatic segments on to the region p13. If the translocation of euchromatic regions is excluded, satellite mutations are without genetic relevance.

3.3 Nucleolus Organising Regions (NOR-Region)

The nucleolus is a cell structure which can be observed in the nucleus during interphase and which is dissolved in the prophase of mitosis and newly synthesised after termination of mitosis. It is the locus of chromosomal r RNA synthesis and is localized in the nucleolus organizing regions (NOR) in the short arms (p12) of the acrocentric chromosomes. During transcription it is decondensed. It is built up by different gene families, only part of them are active in transcription. Mutations in these regions are deletions, duplications, amplifications, and translocations. Translocations are mainly terminal but interstitial insertions are also diagnosed. The chromosomes most frequently involved are 1, 2, and 4. Mosaic cases of postzygotic origin have been observed.

A secondary change to genetic relevant mutations can take place by an unequal crossing over in meiosis. If the insertion of the NOR-region leads to disruption of a tumor suppressor gene it can induce tumor genesis.

Genetic counseling has to be offered in familial cases and in the prenatal period then the indication for microarray analysis is given.

3.4 Pericentromeric Heterochromatin

All human chromosomes are built up from different types of heterochromatin distal from the centromere (p11.1, and q11.1 and p11.2 in the acrocentrics). The size of these regions shows interchromosomal differences and can even vary in the single chromosome (i.e. 15q11.1). The band p11.2 in acrocentrics is characterised by its variation in staining intensity (QFQ and DA/DAPI). The pericentromeric regions consist of satellite DNA, β in p11.1 and q11.1 and of the fractions I, II and III in p11.2. Mutations in these regions are very frequent as they have no negative effect on the carrier. Structural mutations are deletions, duplications, inversions and translocations. The different types of mutations show a different intra- and inter-chromosomal frequency. Pericentromeric mutations in chromosome 18 can be of diagnostic relevance. Especially deletions can lead to a misinterpretation of interphase-FISH. Therefore some diagnostic centers for prenatal aneuploidy screening changed the 18cen probe for a euchromatic probe in 18q.

3.5 Centromere

The centromere is a complex structure of highly repetitive DNA. Its position in the chromosome presents as primary constriction of meta-, submeta- and acrocentric chromosomes. In interphase the centromeres remain more condensed than the rest of the chromosome. Special staining is performed by CBG and DA/DAPI banding, the active centromere in dicentric chromosomes can be characterised by Cd-staining. Centromeres have a complex structure of central elements (α-satellite DNA), distal followed by repetitive regions and laterally associated of the protein complex of the kinetochore. In meristematic cells the combination of centromere and kinetochore is necessary for the correct separation of the chromatids in anaphase of the mitosis, up to this phase the centromere saves the chromatids from premature separation. A high number of mutations in the centromere regions have been observed. Besides deletions, duplications, amplifications and translocations, splitting of the centromere in inversions, fusions, fissions, insertions and centromere-telomere fusions are diagnosed, as well as cases of premature separation of the centromere. Instability of the centromere structure can lead to the development of a multiradial structure or to premature separation (i.e. Roberts syndrome). Centromere mutations are of genetic relevance, therefore genetic counseling should be offered to the carrier.

3.6 Heterochromatic Blocks

Large heterochromatic regions or blocks are a characteristic feature in the autosomes 1, 9, 16 with position proximal in 1q12, 9q12, 16q11.2 and distal in the long arm of the Y-chromosome (Yq12). Less extended blocks visualized by QFQ-banding are 3q11.2 and 4q11.2. The heterochromatic blocks contain about 10% of the human genome. During the cell cycle they are late replicating. The regions in 1q12 and 9q12 are built in 2 parts which is the reason for the frequency of partial inversions.

In interphase the heterochromatin blocks tend to develop fusions. They are preferential positions for breaks and rearrangements. It is assumed that they have a regulatory function in the cell. Special staining methods are CBG, QFQ and DAPI. The heterochromatic regions consist of highly repetitive DNA of the classes Sat I to IV. Mutations in the regions are deletions, duplications, amplifications and partial or complete inversions. These rearrangements are frequent in chromosomes 1, 3, 4, 9 but rare in 16. Interchromosomal rearrangements are translocations and insertions.

They are analysed to differ between mono- and dizygotic twins, to characterise specific ethnic groups, to differ between donor and recipient after bone marrow transplantation, in the analysis of complete moles and in cases of chimerism.

Up to our present knowledge mutations in heterochromatic regions are usually without genetic relevance. After homogenous staining (Giemsa, Orcein) the chromatids show an increased contraction of the heterochromatic blocks. The size of these regions can amount up to 35% of the total length of the chromosome with this type of heteromorphism.

Proximal of these blocks in the autosomes they are followed by the heterochromatic band q11.1, distal by the euchromatic GC-rich band in q13. In the majority of cases pericentric inversions concerning these regions are stable when inherited. An exception is observed in chromosome 9. In single cases when the breakpoint in the long arm is within the band q13 this can lead to an unequal crossing over in meiosis and thus to partial euchromatic duplications or deletions in the progeny resulting in a characteristic phenotype. In these special cases diagnostic investigations afford microarray analyses.

Single Case Presentations

4

4.1 Introduction

A total of 88 chromosome aberrations is presented in detail. For each type of abnormality the cases are summarised and the relevant facts are discussed. In the single case the karyotype is described and illustrated in detail, the indication for chromosome analysis is given, the morphology of the aberrant chromosome(s) is noted including the necessary resolution for receiving a reliable diagnosis.

It is explicitly stated for each case, if special facts have to be taken into account when the patient and/or his family are recommended genetic counselling. If additional investigations are required, this is noted in detail.

As an example, in a total of 10 cases frequent variants of the chromosomes—we chose pericentric inversions of the heterochromatin blocks 1, 3, 4, 9—with changes of their position from the q- to the p-arm were given. This is to give the reader an impression on the altered phenotype of the chromosome and on the investigation method, which has to be chosen to analyse them (CBG- or QFQ-banding).

4.2 Structural Chromosome Aberrations

4.2.1 Intrachromosomal Rearrangements

4.2.1.1 Inversions

The indication for chromosome analysis was infertility in all cases, therefore this item is not mentioned in the detailed case presentations.

Pericentric Inversions

1 46,XY,inv(1)(p12q12),inv(1)(p13.1q21)
2 46,XY,inv(2)(p11.2q13)
3 46,XY,inv(3)(p12.2q26.32)
4 46,XX,inv(4)(p12q21.1)
5 46,XY,inv(5)(p15.1q33.2)
6 46,XY,inv(5)(p13.2q13.2)
7 46,XY,inv(7)(p10q11.23)
8 46,XX,inv(7)(p22q34)
9 46,XX,inv(8)(p11.2q21.12)
10 46,XX,inv(10)(p11.2q21.2)
11 46,XY,inv(11)(p13q21),inv(9)(p12q12)
12 46,XX,inv(16)(p13.2q11.1)
13 46,XY,inv(16)(p12q12.2)

C. Behrend et al., *Human Chromosome Atlas*,
DOI 10.1007/978-3-319-54099-3_4

14 46,XX,inv(20)(p13q13.2)
15 46,X,inv(X)(p22.1q26)
16 46,X,inv(X)(p22.13q24),inv(3)(p11.2q12)
17 46,X,inv(Y)(p11.2q11.23)

Case 1: Karyotype: 46,XY,inv(1)(p12q12),inv(1)(p13.1q21)

The proband shows pericentric inversions in both homologues chromosomes.
Morphology:

1. inv(1)(p12q12)
   The breakpoints of this proximal inversion are both located in heterochromatic regions. In the short arm the breakpoint is in p12 the pericentromeric heterochromatin and in q12 in the heterochromatic block which is thus translocated into the short arm. This inversion is known as a polymorphism without genetic relevance. The region encloses 8–15% of the total length of chromosome 1, its frequency in the European population about 1‰ (see: Chap. 2.6).
2. inv(1)(p13.1q21)
   Presented is very small proximal pericentric inversion. The inverted segment comprises about 7% of the total length of chromosome 1. As the heterochromatic block q12 has a high interindividual variation in length, an inversion with differing heteromorphisms can result in a different proportion of the rearranged region. One breakpoint is localised in the GC-rich band p13.1, the second one in the proximal part of the heterochromatic block q12. Here a euchromatic polymorphic band is located which is a preferential breakpoint in pure heterochromatic inversions, as it is presented in the second chromosome 1 of the carrier.
   Beside GTG- and QFQ-banding CBG staining is required for the presentation of the inversion. A resolution of at least 550 bands per genome is necessary for the diagnosis of the rearrangement.

Cave:

Compared to inversions with similar size but both breakpoints in euchromatic segments the genetic risk is reduced in the present case where one breakpoint is located in an heterochromatic region (Fig. 4.1).

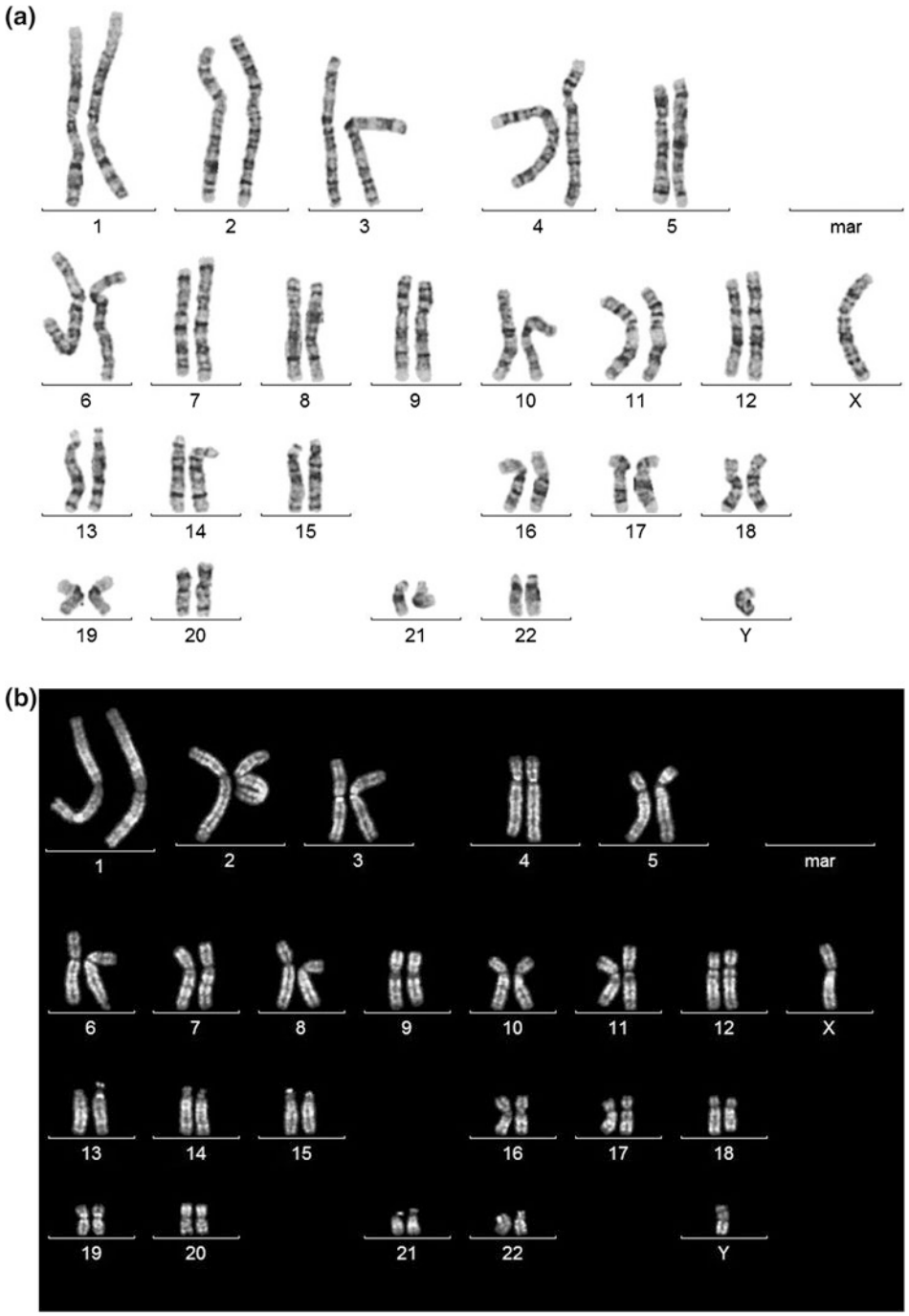

Fig. 4.1 Karyotype 46,XY,inv(1)(p13.1q21),inv(1)(p12q12). **a** GTG-banding, **b** QFQ-banding, 550- and 400-bands per genome, **c** CBG-banding, **d** QFQ-banding, **e** GTG-banding, chromosomes from different mitoses; *left* inv(1)(p13.1q21), *right* inv(1)(p12q12), **f** ideograms of case 1. Both homologues show a pericentric inversion, *left* breakpoints in heterochromatic regions, *right* breakpoints in the euchromatin

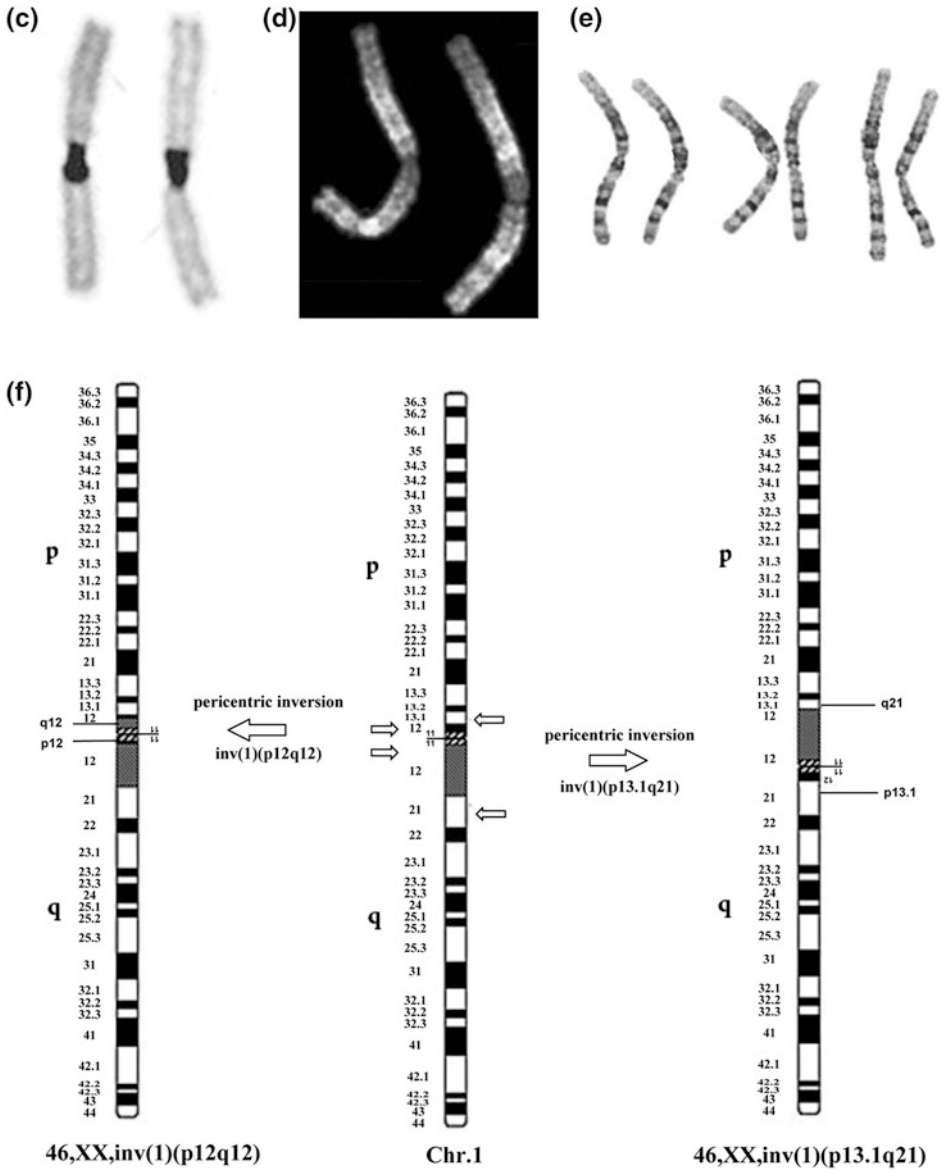

Fig. 4.1 (continued)

Case 2: Karyotype: 46,XY,inv(2)(p11.2q13)
Morphology:

The pericentric inversion 2 presented here is the most frequent one, excluding pure heterochromatic inversions, with about 1:1300 but significant differences in different ethnic groups (lowest frequency 1:10,000). The breakpoints are localised in regions of common fragile sites. Molecular genetic analyses have shown that the breakpoints are not always quite identic. The inverted region comprises about 5% of the total length of chromosome 2. This inversion is recognised by dislocation of the AT-rich band q13 from the long into the short arm. The exact breakpoint localisation affords a resolution of at least 550 bands per genome.

Cave:

More than 95% of the published cases are of familial origin. For many years this type of chromosome 2 inversion was thought to be stable when inherited, as no carrier of an unbalanced inversion was diagnosed. Therefore this inversion was often also classified as a polymorphism. But recently two cases were published, one with a partial duplication and one with a partial deletion of the region in question. A genetic risk therefore cannot be excluded, although it can be defined to be very low (<1%) (Fig. 4.2).

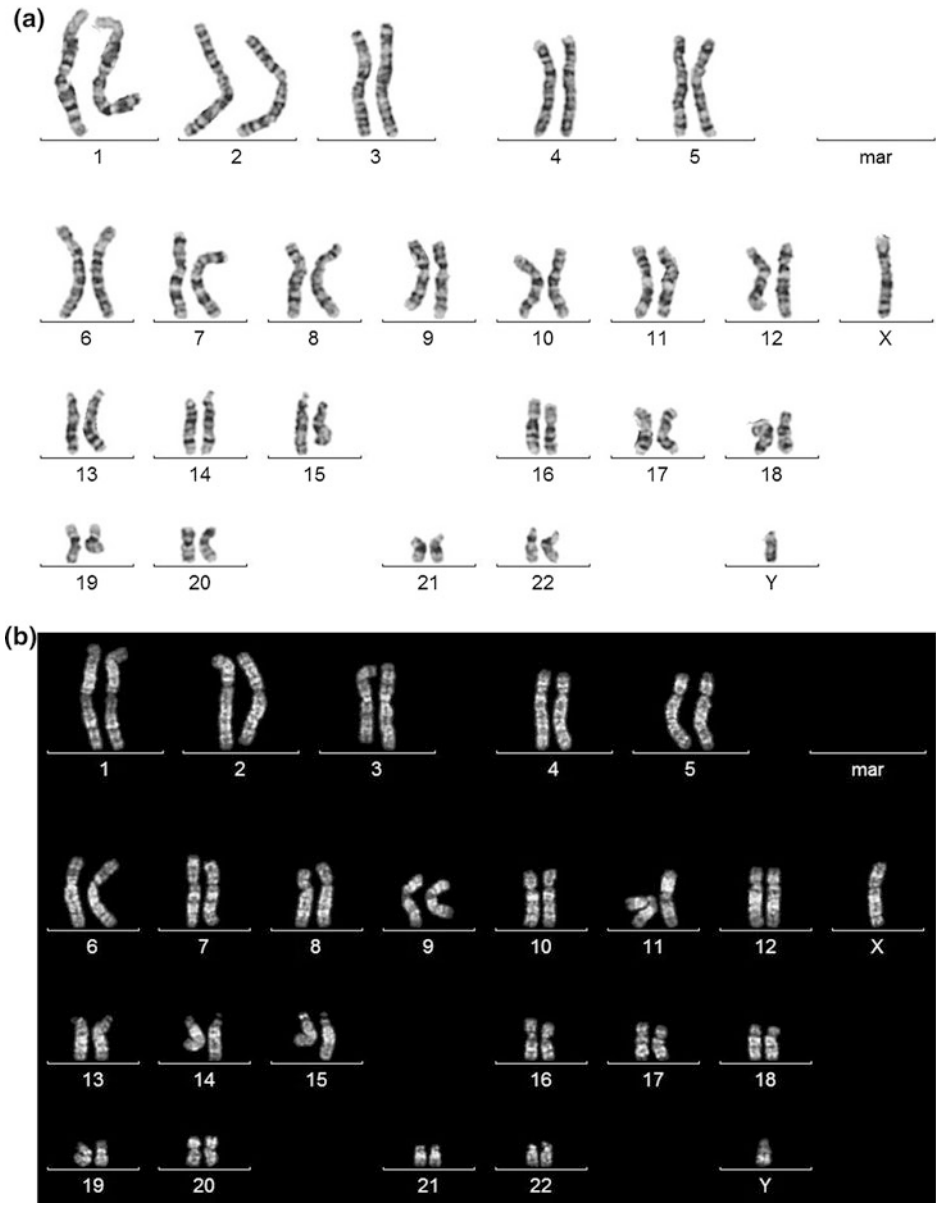

Fig. 4.2 Karyotype 46,XY,inv(2)(p11.2q13). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 2, **e** Ideogram of case 2, small proximal inversion

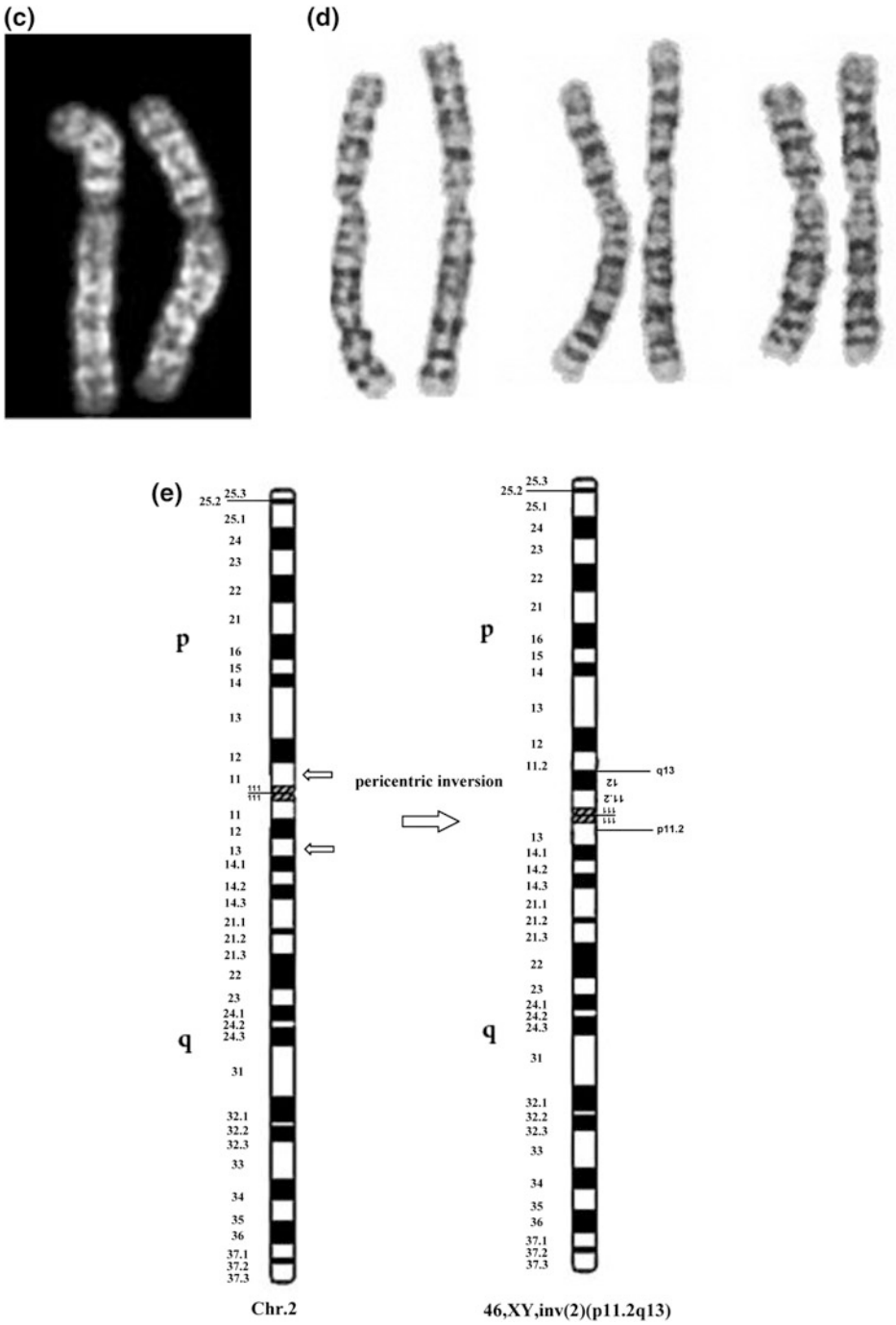

Fig. 4.2 (continued)

Case 3: Karyotype: 46,XY,inv(3)(p12.2q26.32)
Morphology:

This pericentric inversion comprises about 50% of the total length of chromosome 3. The most prominent change in the chromosome morphology is an altered centromere index from a proportion of short and long arm of 48:52% to 17:83%. The broad AT-band p12, proximal located in the shortened long arm is a further relevant criterion for identification. A resolution of 550 bands per genome enables a correct diagnosis. In the presented case an additional CBG-banding improves the investigation. Chromosome 3 is one of the three chromosomes which, according to the literature present with the highest frequency of pericentric inversions.

Cave:

The inverted region comprises about 50% of the total length of chromosome 3, according to literature this causes a genetic risk of average probability of about 10%. Therefore potential inversion carriers in the family should be investigated and the indication for prenatal diagnostics is given (Fig. 4.3).

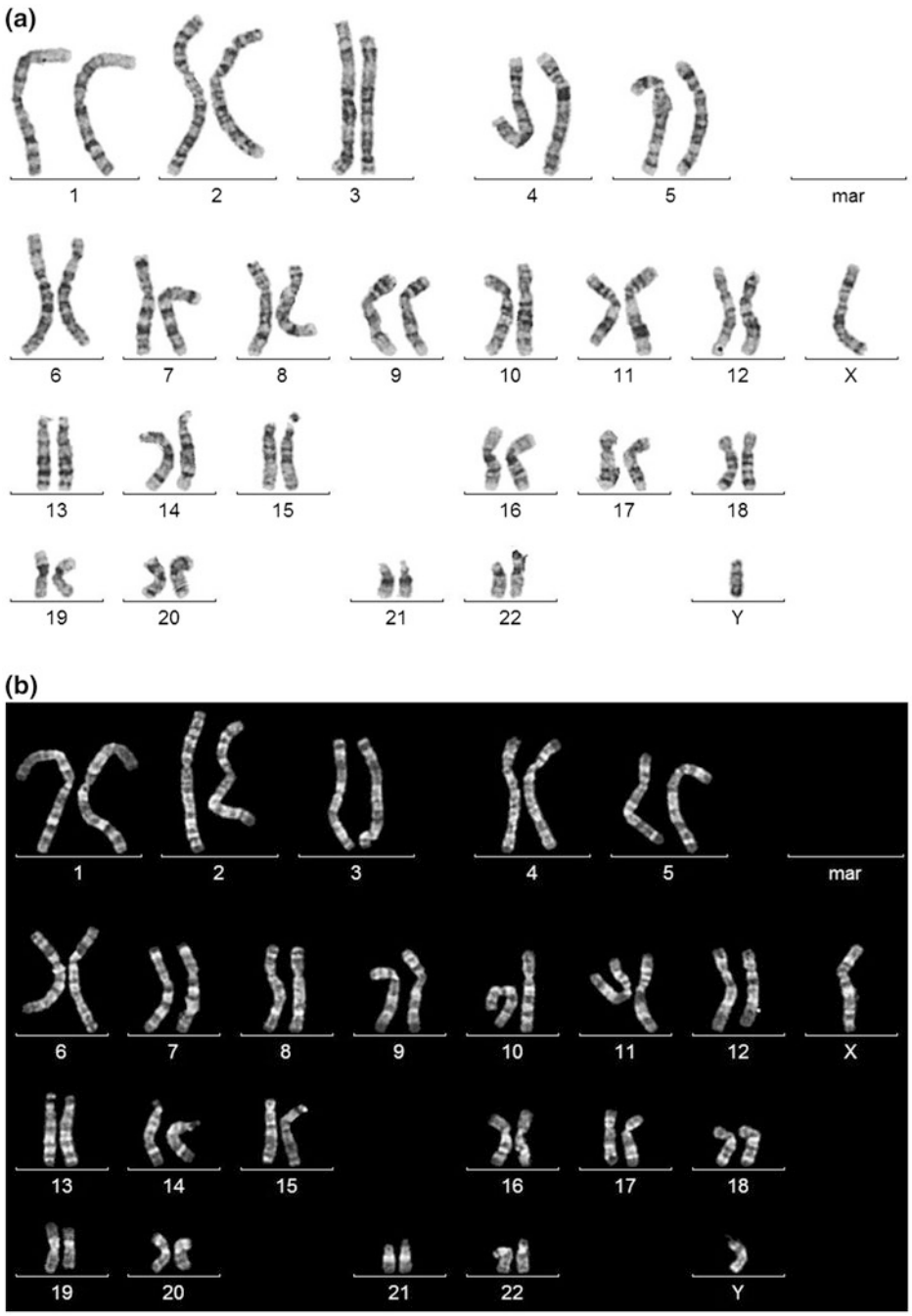

Fig. 4.3 Karyotype 46,XY,inv(3)(p12.2q26.32). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 3, **f** ideograms of case 3, large inverted segment

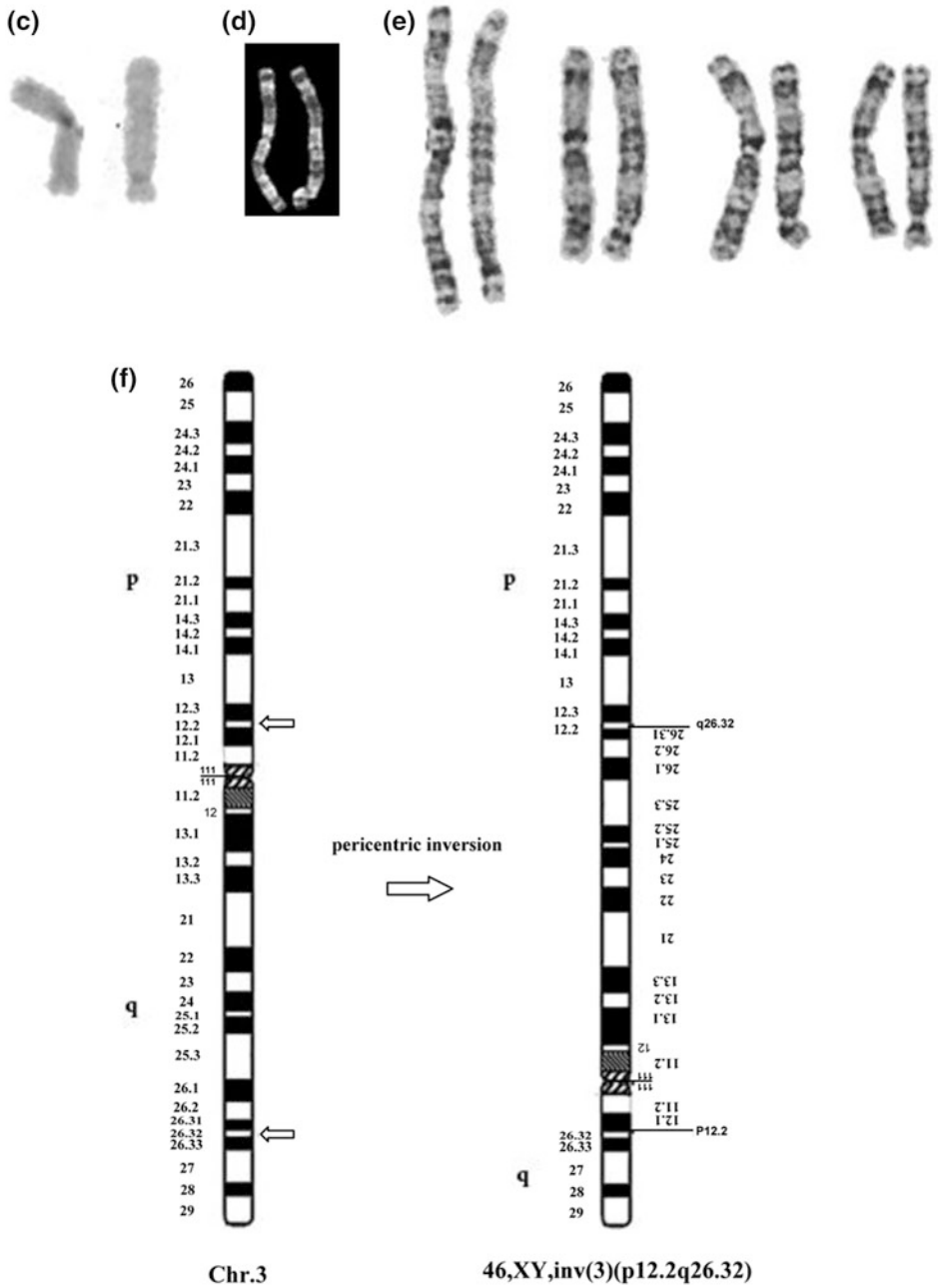

Fig. 4.3 (continued)

Case 4: Karyotype: 46,XX,inv(4)(p12q21.1)
Morphology:

The small pericentric inversion is localised in the proximal segments of the short and the long arm. The inverted region includes only about 16% of the total length of chromosome 4. The analyses of this inversion is easy to perform, as the centromeric index has changed and as the characteristic AT-rich double band q13.1–q13.3 has changed its position from the long into the short arm. Of additional diagnostic relevance in this pericentric inversion is its appearance after QFQ-banding. It shows the shifting of the brilliant fluorescent heterochromatic band 4q11.2 from the long into the short arm.

Cave:

The breakpoints in the short as well as in the long arm are localised in GC-rich regions. Therefore genetic counseling of the carrier is indicated as well as prenatal investigations including microarray to exclude an unbalanced karyotype in the conceptus caused by an unequal crossing over in meiosis (Fig. 4.4).

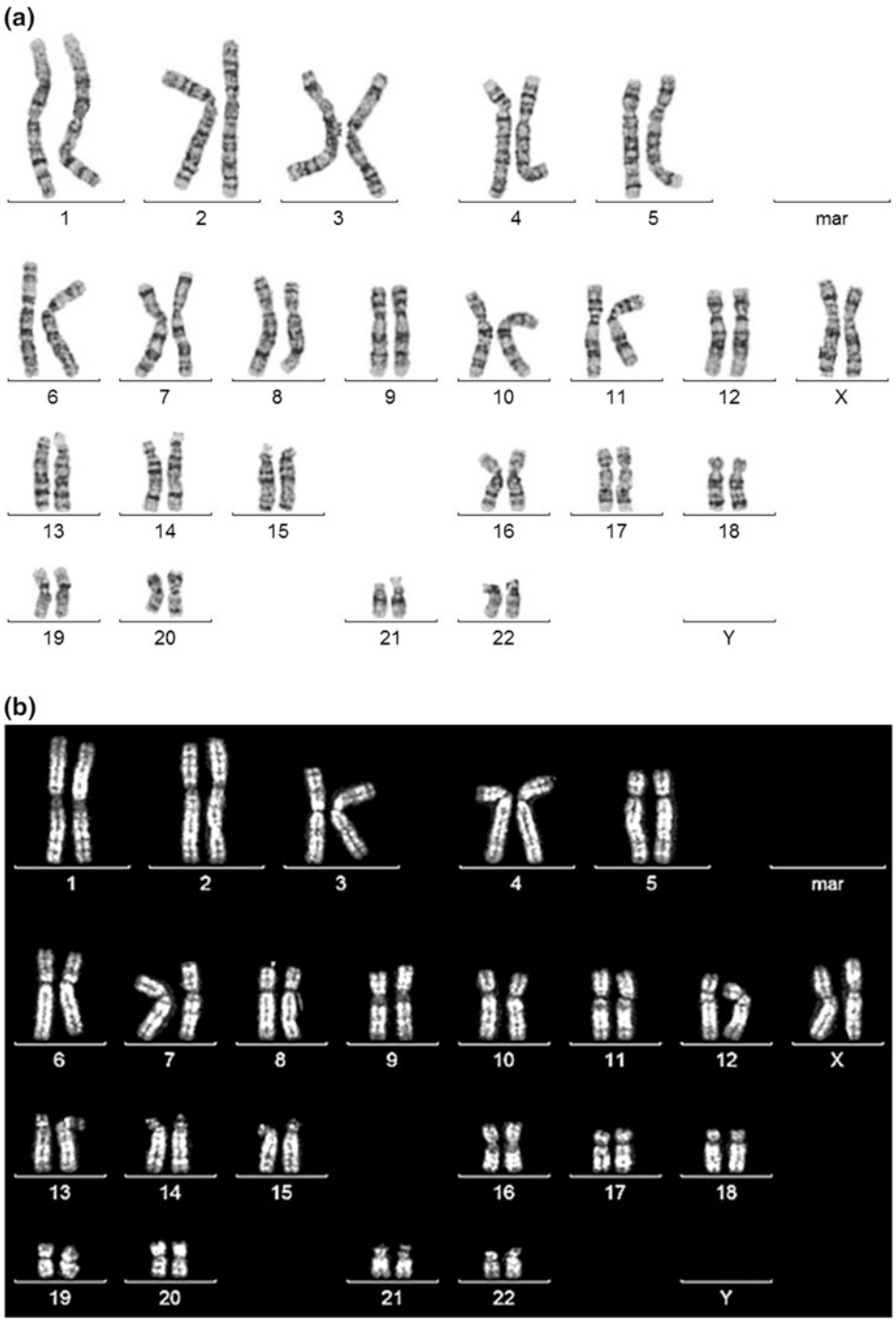

Fig. 4.4 Karyotype 46,XX,inv(4)(p12q21.1). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal chromosome, *right* inverted chromosome 4, **e** ideograms of case 4, small proximal segment inverted

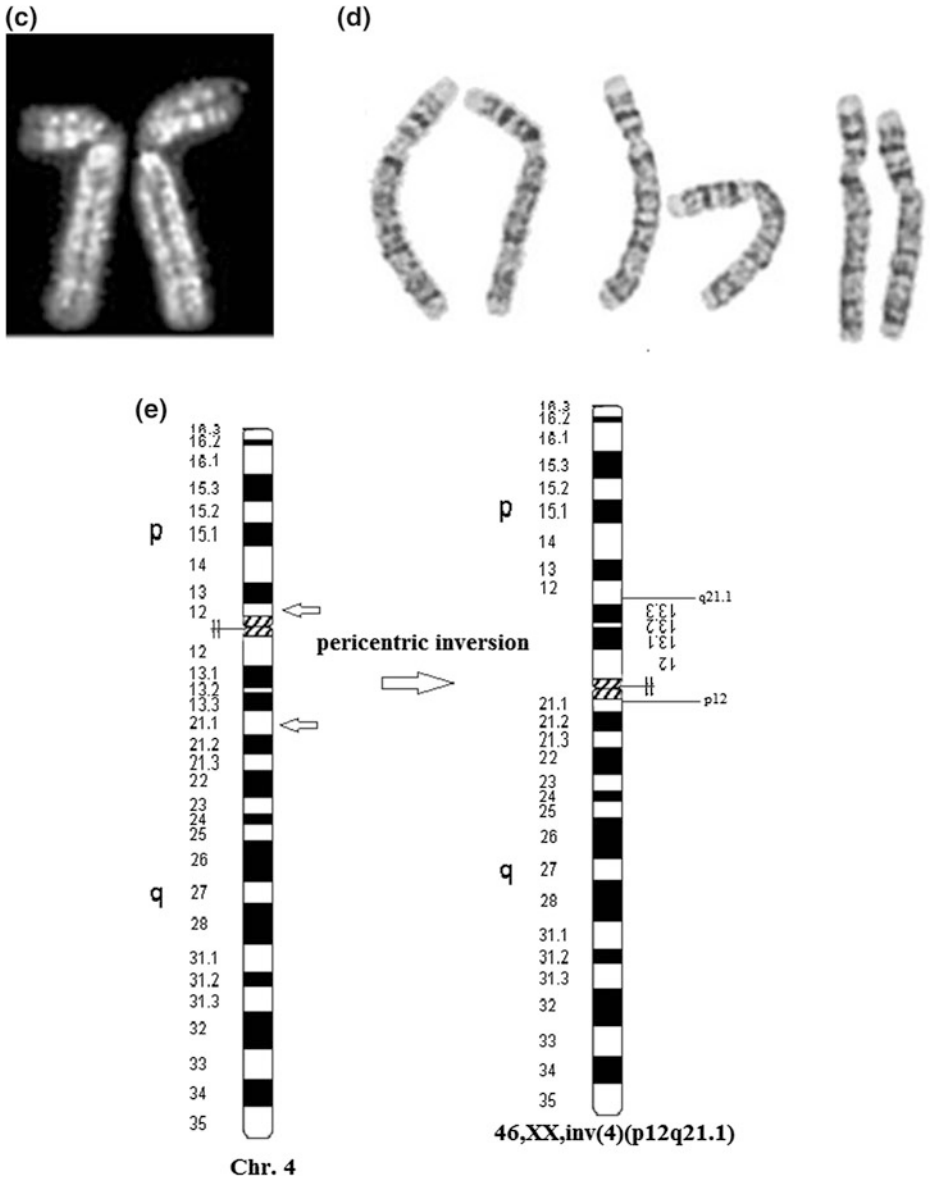

Fig. 4.4 (continued)

Case 5: Karyotype: 46,XY,inv(5)(p15.1q33.2)
Morphology:

The pericentric inversion 5 presented here encloses a region of about 80% of the total length of the chromosome. By the displacement of the centromere the aberrant chromosome has a more metacentric morphology with the arm-ratio changing from 1:28 to 1:2.2. The shifting of the AT-rich band q34 from the long into the short arm leads to a very characteristic change of the banding pattern and thus improves the analysis of the inverted chromosome. The resolution should be at least 550 bands per genome to insure an exact localisation of the breakpoints.

Cave:

Caused by the size of the inverted segment the risk for the formation of an unbalanced karyotype has to be regarded as high with approximately 30%. Prenatal diagnosis including microarray analysis should be recommended. Relatives of the carrier should be offered chromosome investigations. The inversion includes the critical region for the Cri-du-chat syndrome (Fig. 4.5).

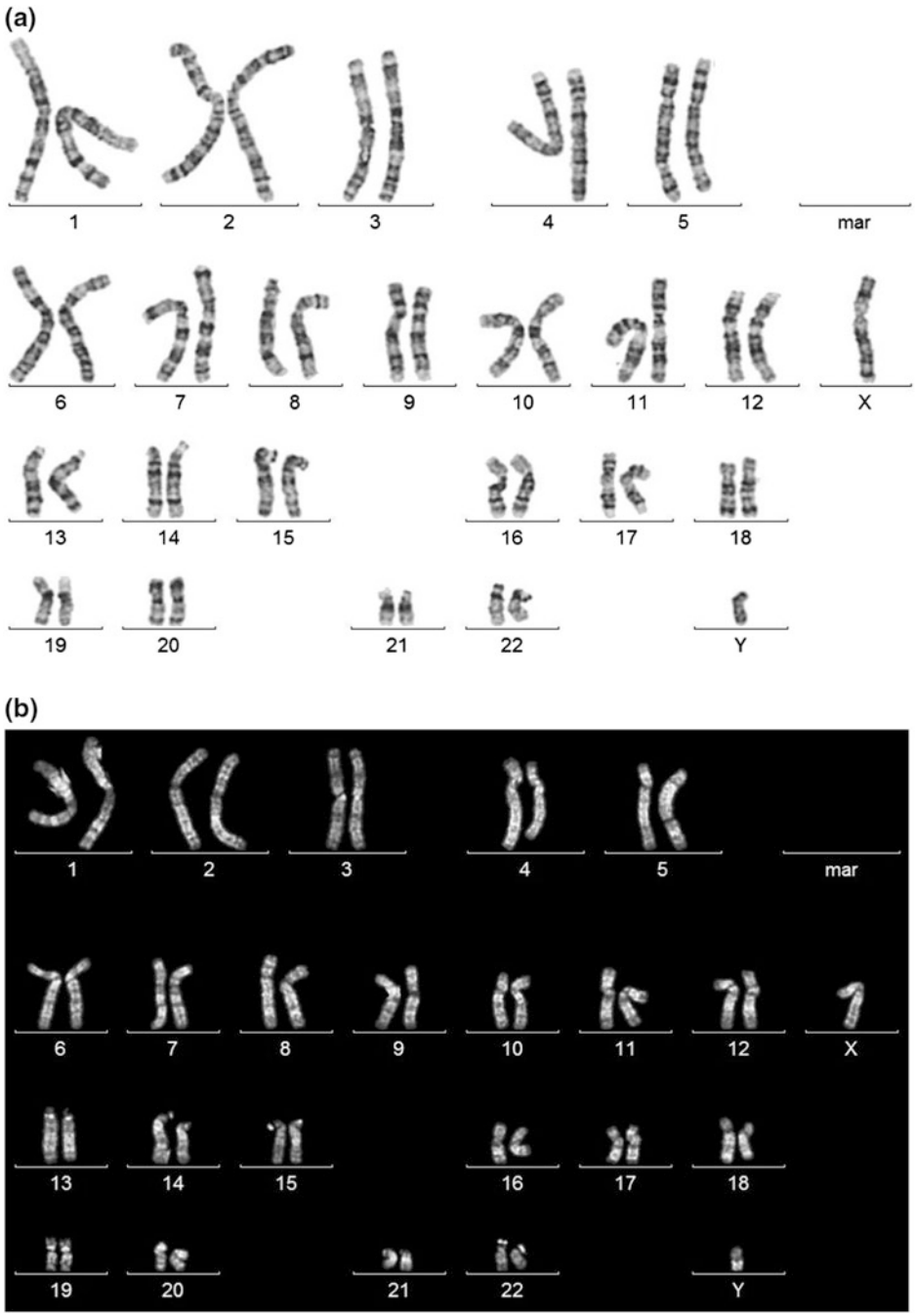

Fig. 4.5 Karyotype 46,XY,inv(5)(p15.1q33.2). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 5, **e** ideograms of case 5, extreme large inverted segment

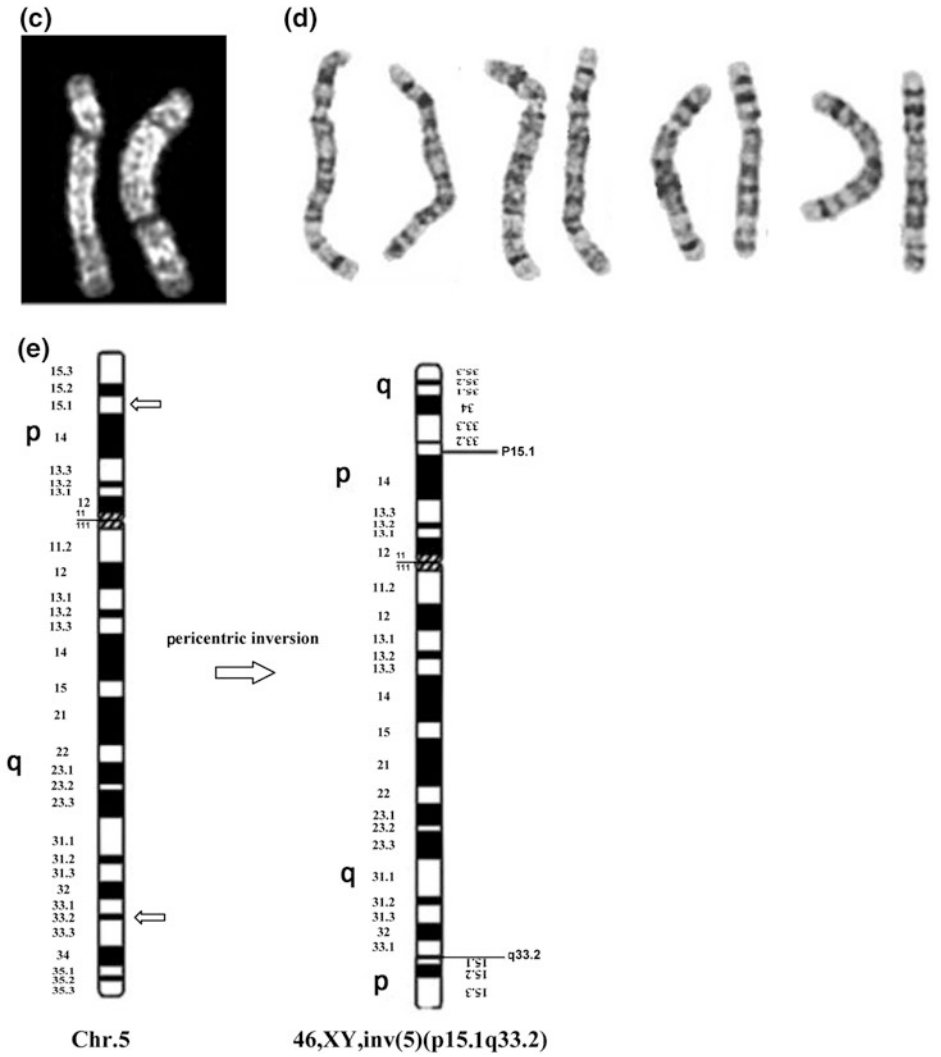

Fig. 4.5 (continued)

Case 6: Karyotype: 46,XY,inv(5)(p13.2q13.2)
Morphology:

The pericentric inversion presented here is characterised by the position of both breakpoints in proximal segments of long and short arm and includes about 18% of the total length of the chromosome. As the breakpoint in the long arm has a more distal position than in the short one the arm ratio has changed, the inverted chromosome appears more metacentric.

Cave:

As the inverted segment is relatively small (about 20%) this is the reason of a low genetic risk. But it has to be taken into account that the Cri-du-chat critical region is included. Therefore the carrier has to be offered prenatal diagnosis and investigations in relatives should be discussed (Fig. 4.6).

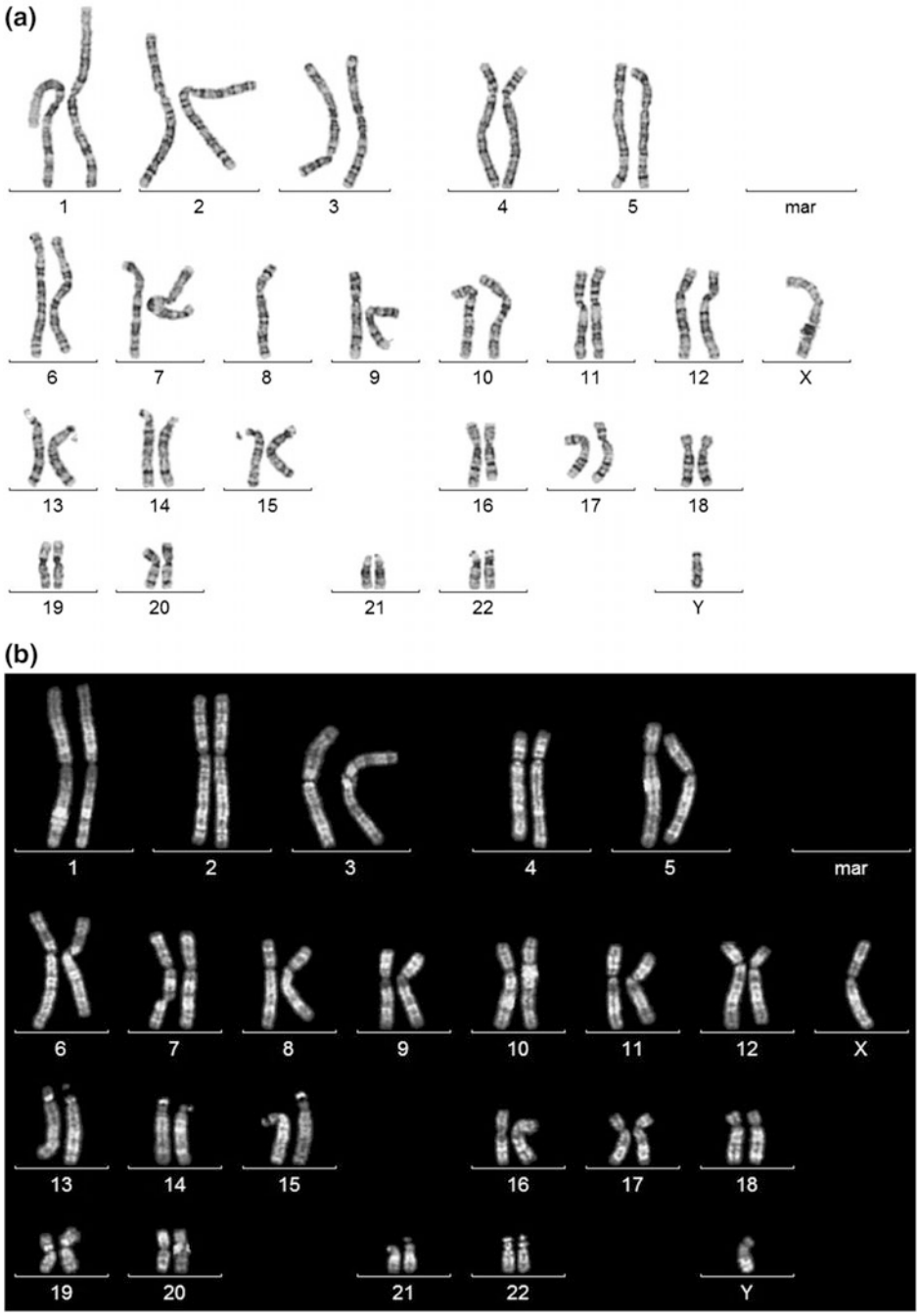

Fig. 4.6 Karyotype 46,XY,inv(5)(p13.2q13.2). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 5, **e** ideograms of case 6, inversion in proximal segments

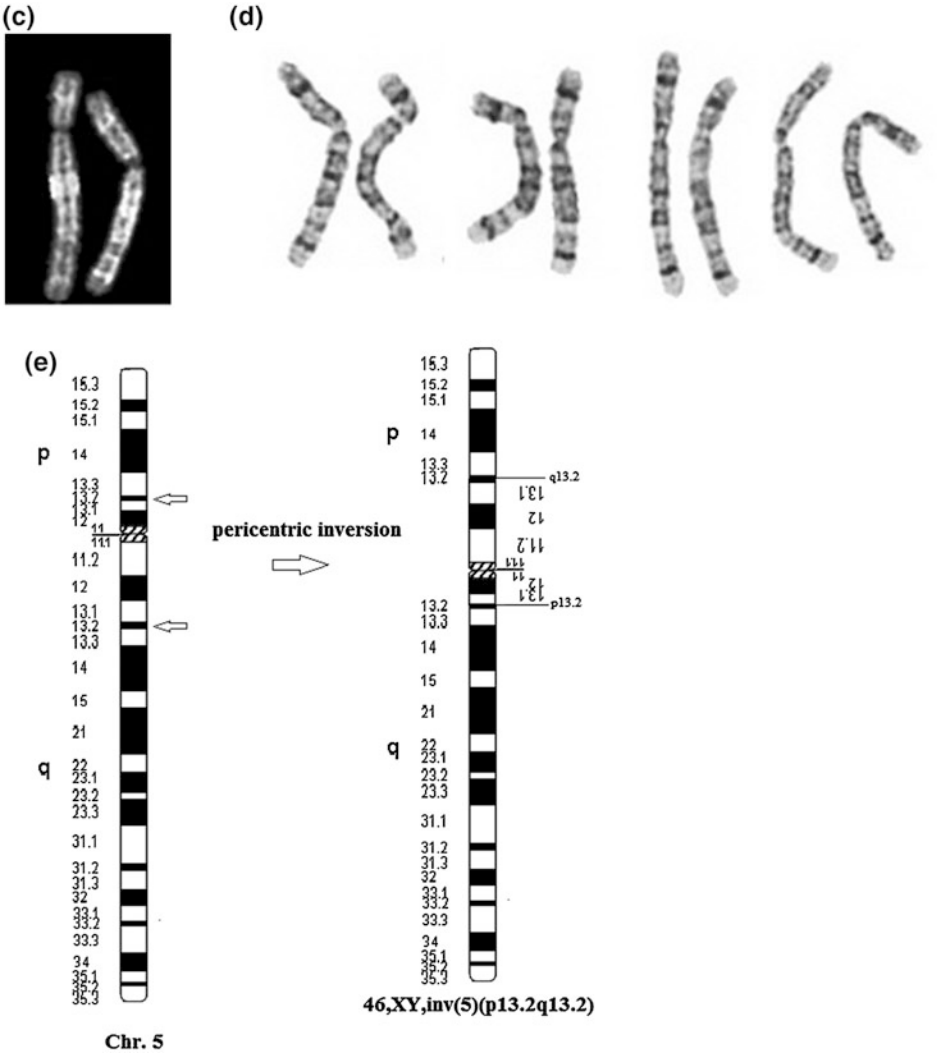

Fig. 4.6 (continued)

Case 7: Karyotype: 46,XY,inv(7)(p10q11.23)
Morphology:

The small pericentric inversion has both breakpoints localised in proximal regions. The breakpoint in the short arm is localised in the pericentromeric heterochromatin. The size of the rearranged segment is about 10% of the total length of chromosome 7. The centromere index has changed from an arm ratio of 34:66% to 48:52%, the inverted chromosome appearing almost metacentric. The inversion is easy to diagnose by the altered centromere index and banding pattern.

Cave:

As one of the breakpoints is localised in the heterochromatic centromere region the risk of an unequal crossing over is lower than in cases with both breakpoints in euchromatic regions (Fig. 4.7).

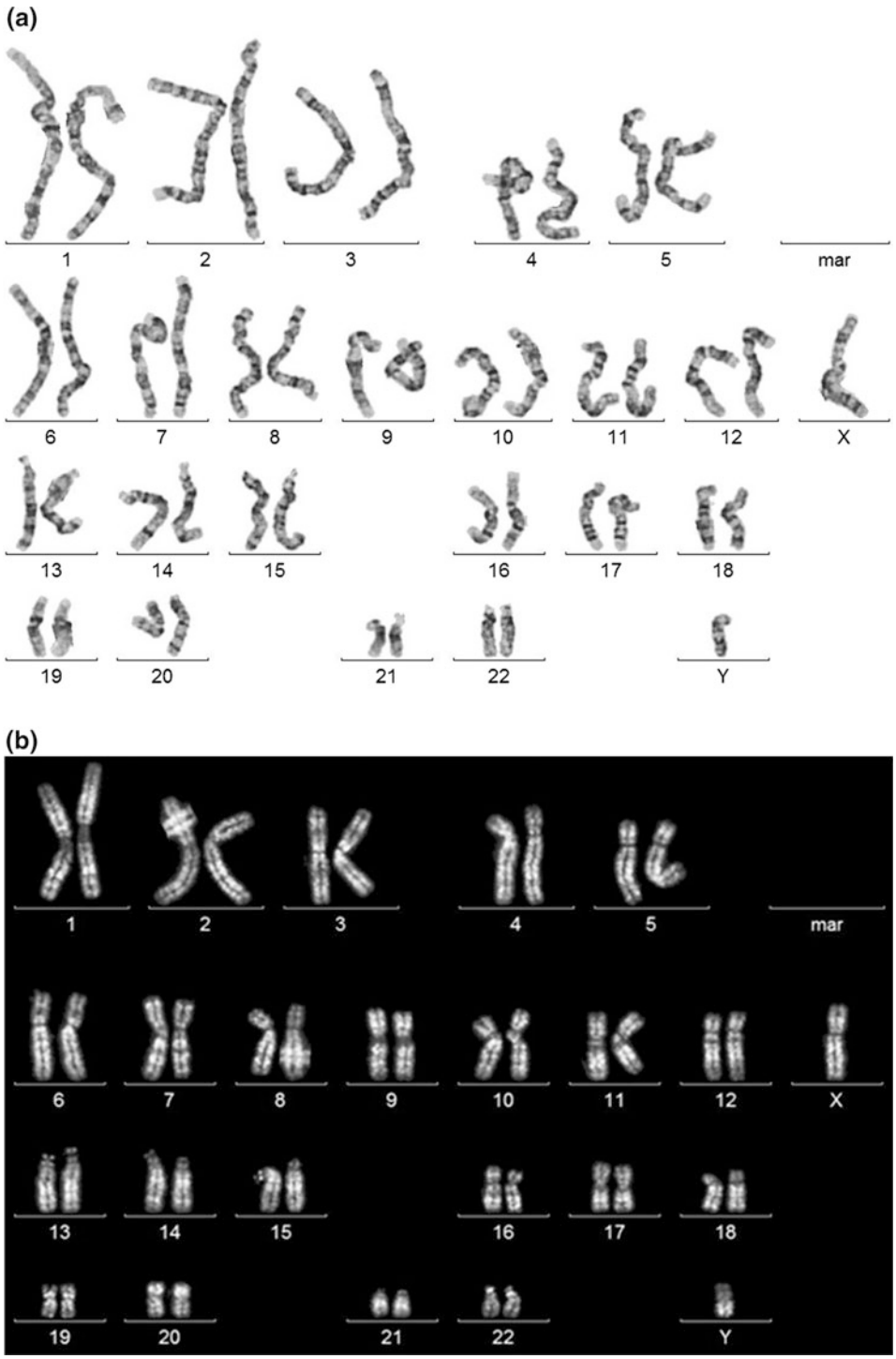

Fig. 4.7 Karyotype 46,XY,inv(7)(p10q11.23). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 7, **f** ideograms of case 7, small inversion with 1 breakpoint in the centromere region

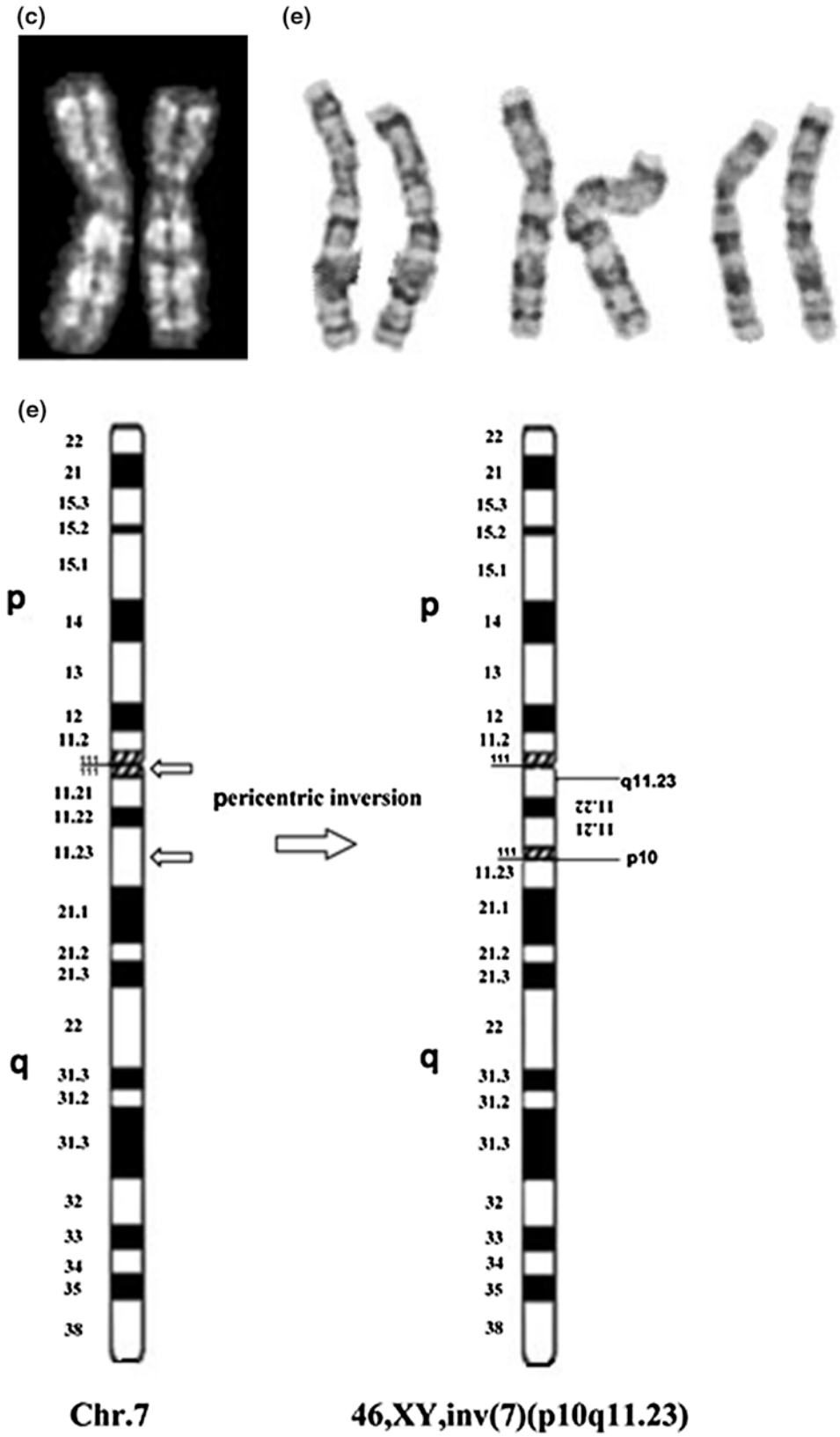

Fig. 4.7 (continued)

Case 8: Karyotype: 46,XX,inv(7)(p22q34)

Morphology:

The inverted region includes about 90% of the total length of chromosome 7. Chromosome 7 belongs to the three chromosomes with the highest frequency of pericentric inversions, the other two are chromosome 3 (case 3) and chromosome 8 (case 9). As it is well known that the risk of an unbalanced rearrangement increases with increasing length of the inverted region, it must be estimated to be about 30%.

Cave:

Because of the high genetic risk chromosome investigations should be offered to relatives of the carrier. To all carriers prenatal diagnoses should be recommended and chromosome analyses are to be combined with microarray investigation. In cases of an aberrant karyotype findings from the literature can be included in genetic counseling (Fig. 4.8).

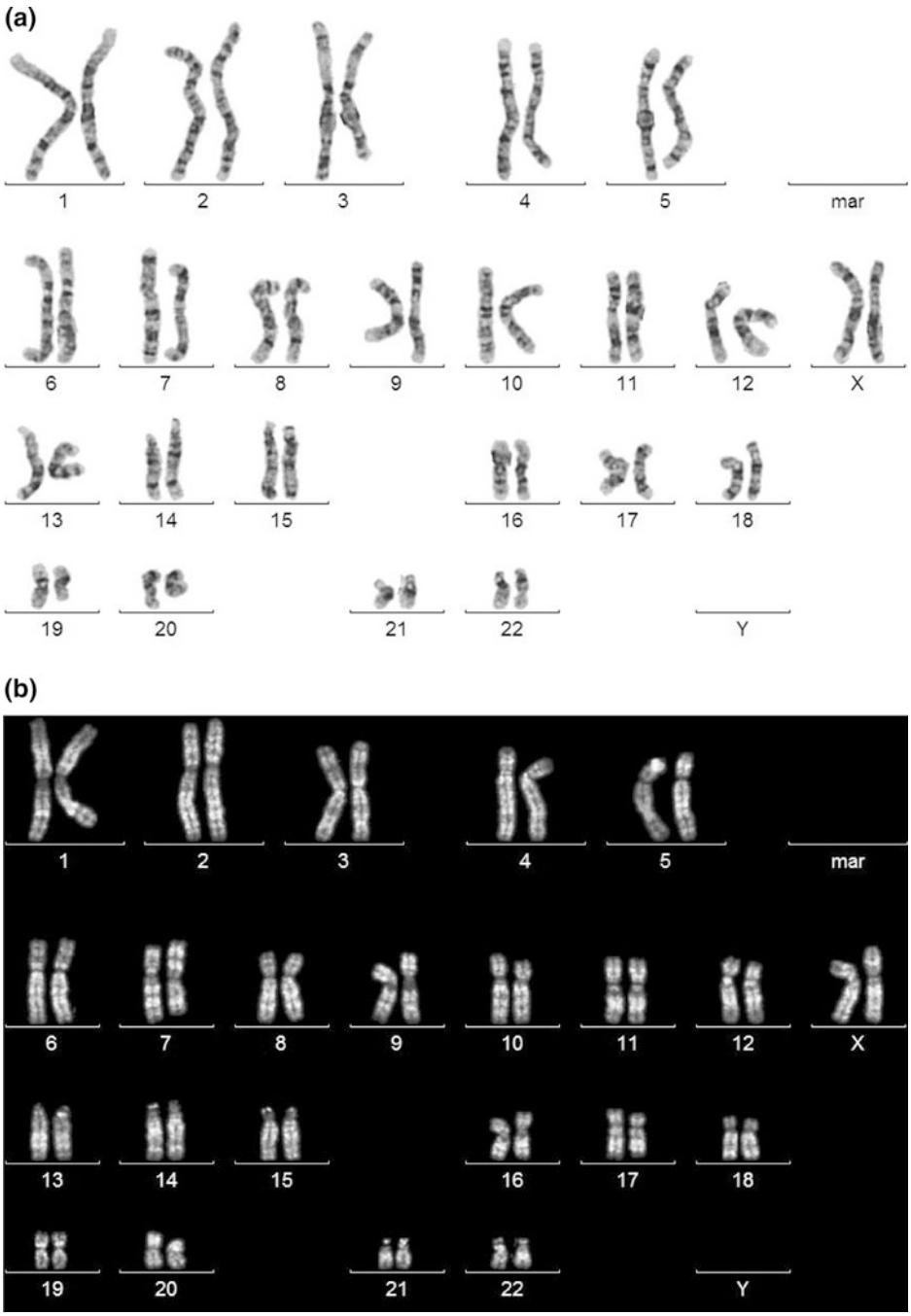

Fig. 4.8 Karyotype 46,XX,inv(7)(p22q34). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 7, **e** ideograms of case 8, extreme large inverted segment

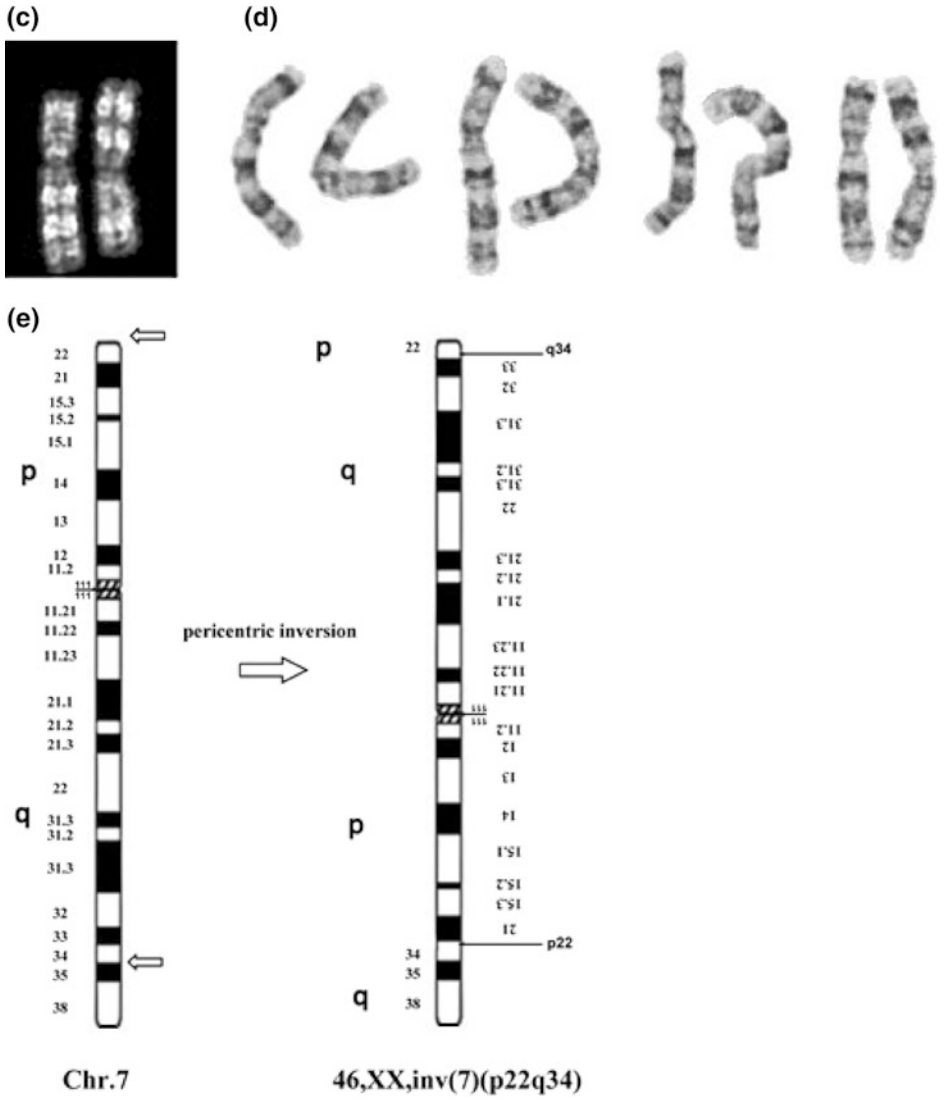

Fig. 4.8 (continued)

Case 9: Karyotype: 46,XX,inv(8)(p11.2q21.12)
Morphology:

The inversion 8 presented here comprises about 25% of the total length of the chromosome. The breakpoint in the short arm is localised in p11.2, a proximal GC-rich band which is neighboring the pericentromeric heterochromatin. The second breakpoint is intermediate in q21.2. Therefore the arm ration p:q has changed from 30:70% to 50:50%. The inverted chromosome appears metacentric. The exact breakpoints can only be determined at a resolution of about 700 bands per genome. This case is a good example that a high banding resolution is required in difficult chromosome rearrangements.

Cave:

Investigations on pericentric inversions of comparable size lead to an intermediate genetic risk for the carrier. Genetic counseling and prenatal diagnoses are indicated (Fig. 4.9).

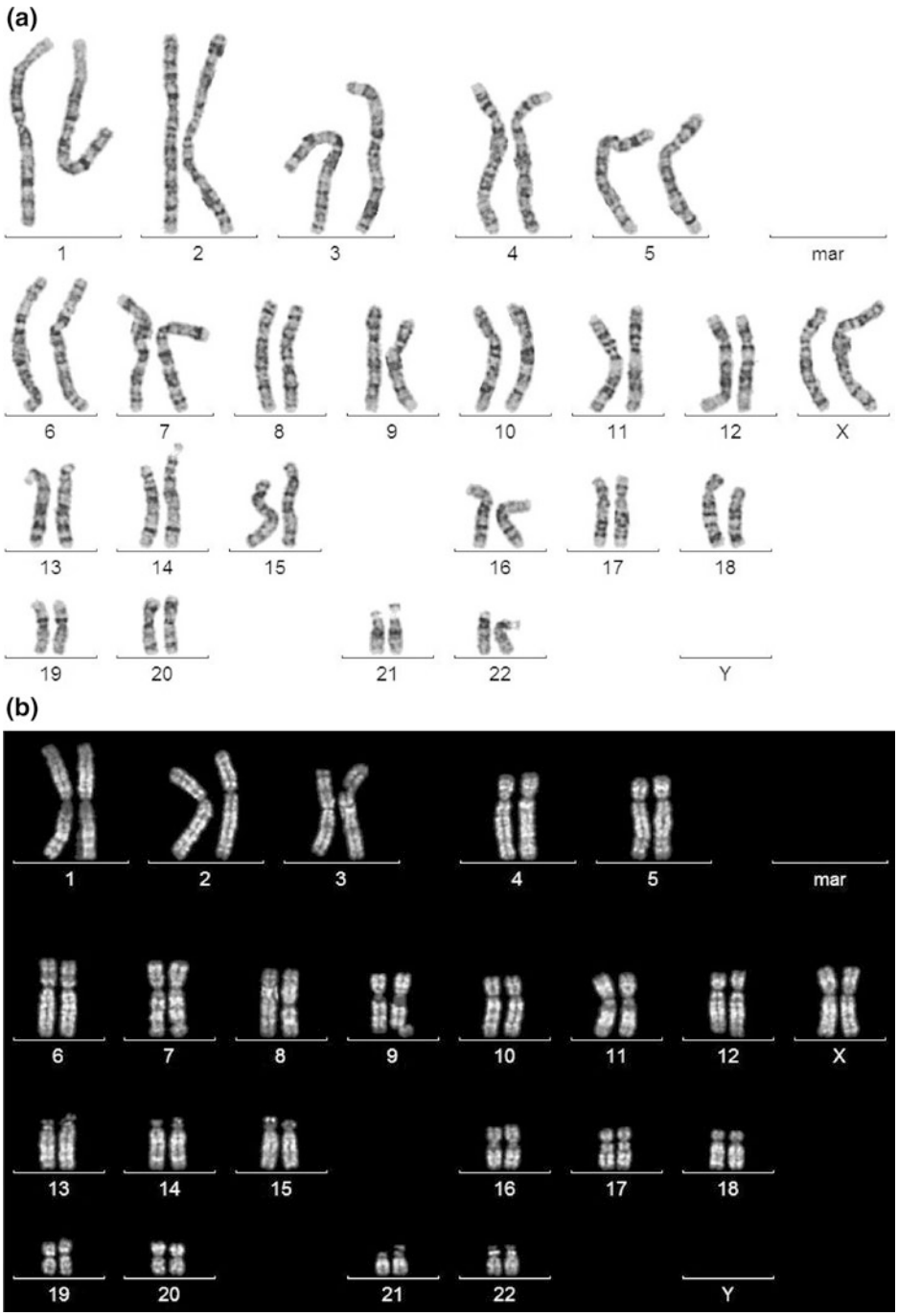

Fig. 4.9 Karyotype 46,XX,inv(8)(p11.2q21.12). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 8, **e** ideograms of case 9, inverted segment is medium in size

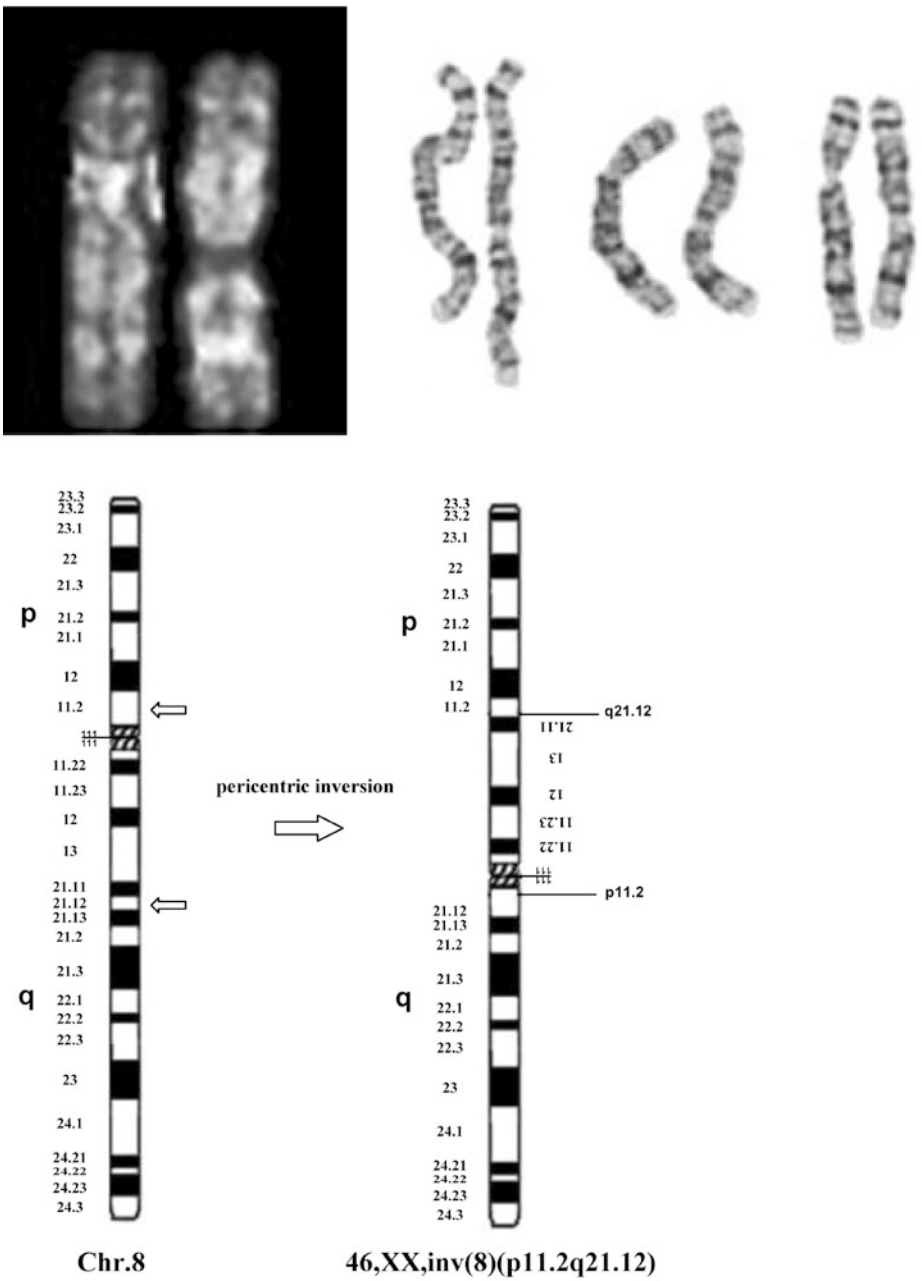

Fig. 4.9 (continued)

Case 10: Karyotype: 46,XX,inv(10)(p11.2q21.2)
Morphology:

This inversion is a stable chromosome rearrangement which is, according to the literature, inherited in the families involved without occurence of unbalanced karyotypes. The inverted region comprises about 20% of the total length of the chromosome. The dislocation of the AT-rich band q21.1 changes the banding pattern in a characteristic way, so that this inversion is easy to diagnose.

Cave:

Therefore when analysing this type of inversion, family investigations or prenatal analyses must not be recommended (Fig. 4.10).

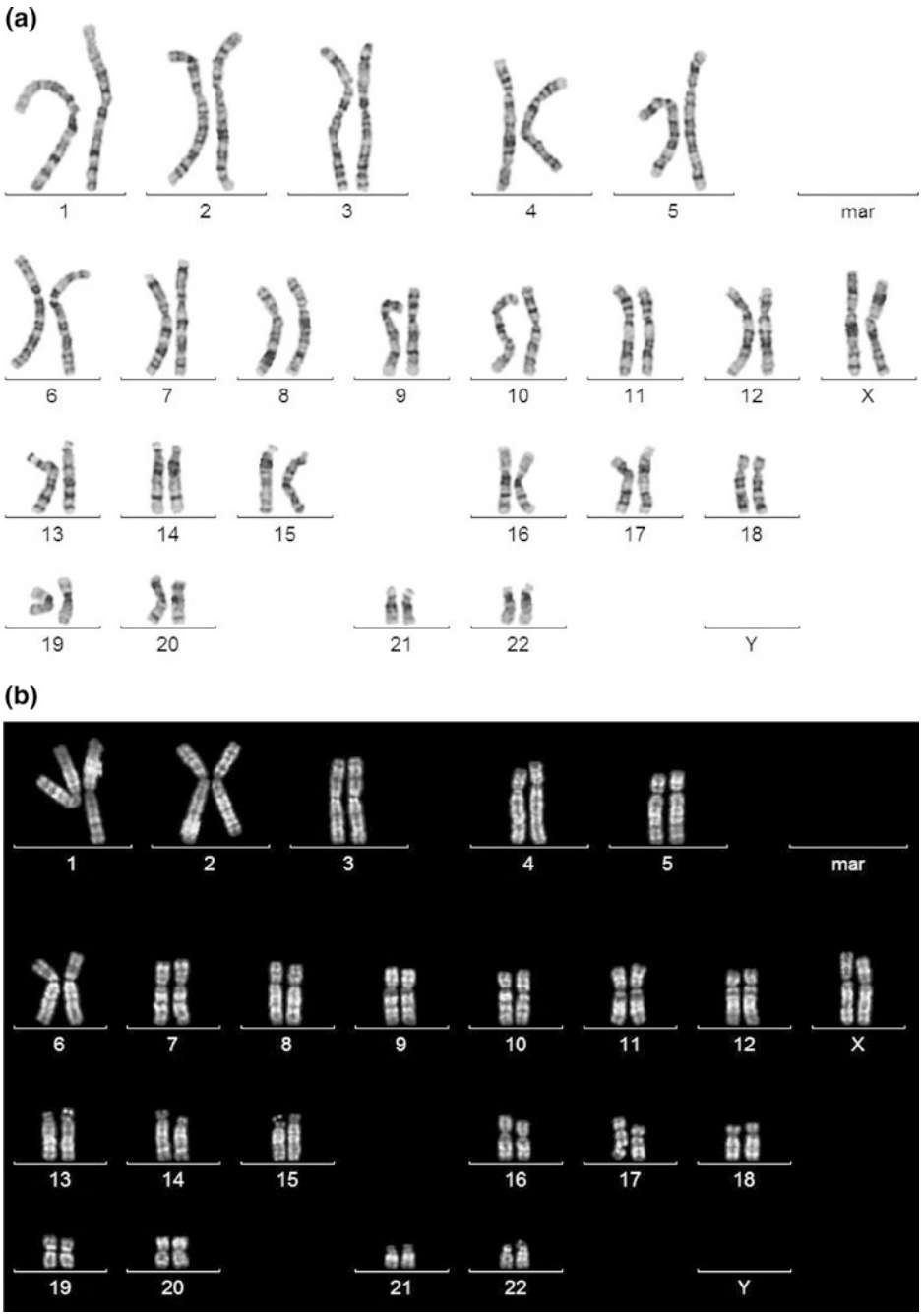

Fig. 4.10 Karyotype 46,XX,inv(10)(p11.2q21.2). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 10, **e** ideograms of chromosome 10, proximal breakpoints of the inverted segments

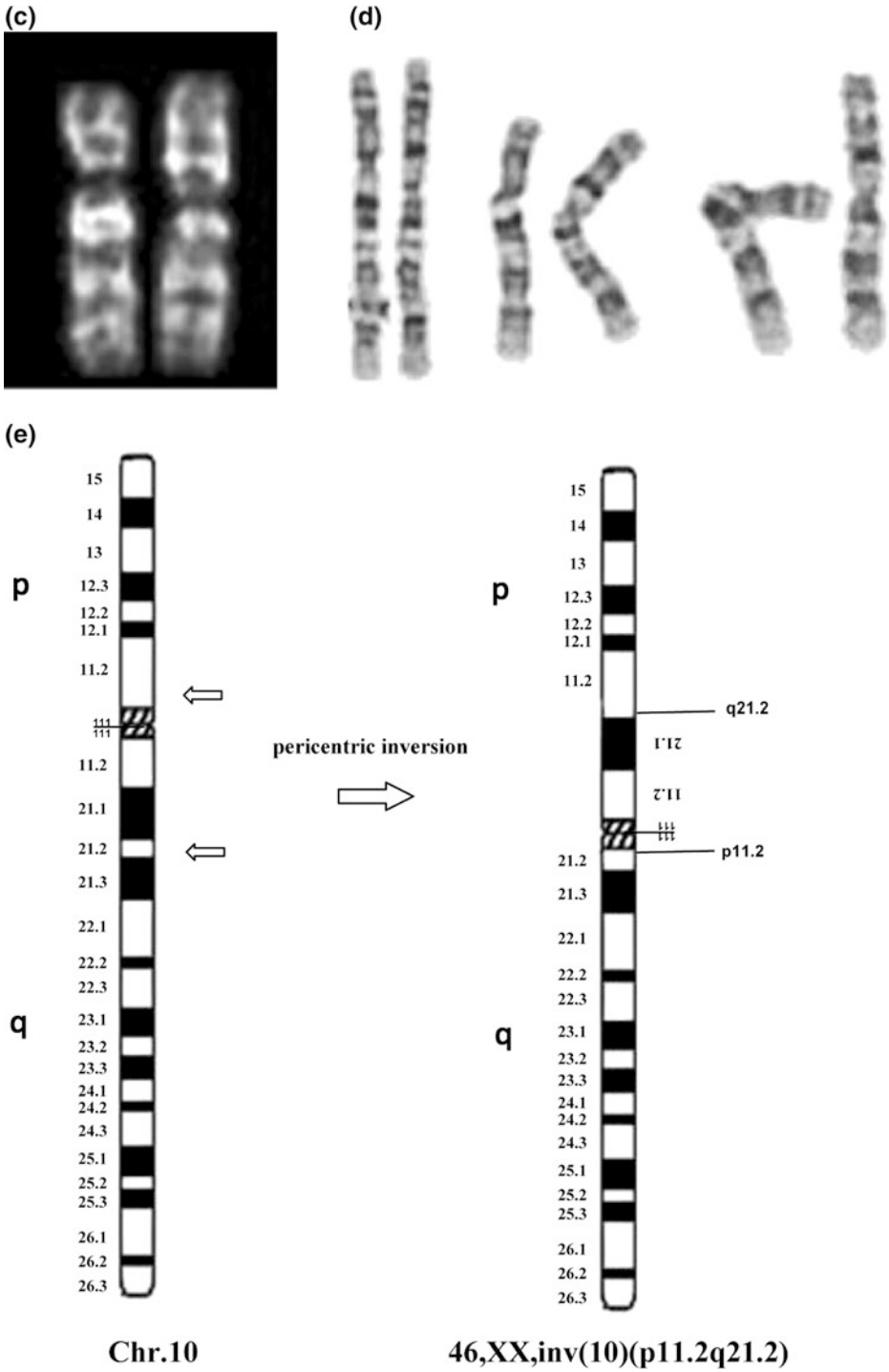

Fig. 4.10 (continued)

Case 11: Karyotype: 46,XY,inv(11)(p13q21),inv(9)(p12q12)
The proband presents with two pericentric inversions.

Morphology:

1. inv(9)(p12q12): Type II
   The breakpoints of this pericentric inversion are both localised in heterochromatic segments. The heterochromatic block q12 has been shifted into the proximal short arm region. This type of inversion is defined as polymorphism without genetic relevance. Its frequency in the European population is about 1% (see: Chap. 2.6).

2. inv(11)(p13q21)
   This pericentric inversion comprises about 50% of the total length of chromosome 11, both breakpoints are located in intermediate regions. The analysis of the rearrangement is easy to perform because of the dislocation of the AT-rich band q14 from the long into the short arm.

Cave:

Genetic counselling after investigation of the relatives includes recommendation of prenatal investigations. But according to the literature this inversion seems to be stable when inherited and the genetic risk might be small (Fig. 4.11).

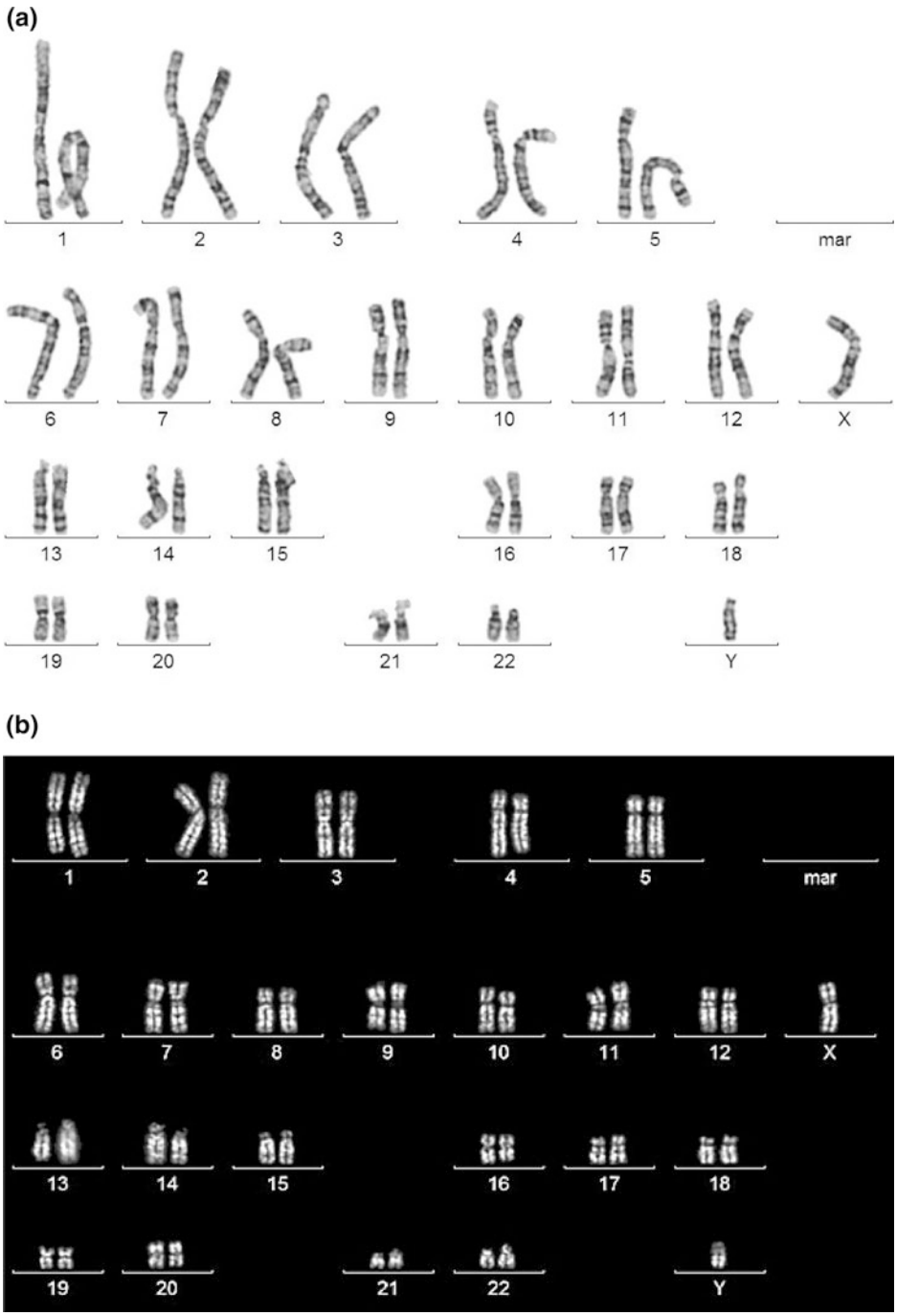

Fig. 4.11 Karyotype 46,XY,inv(11)(p13q21),inv(9)(p12q12). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, chromosome 9: *left* normal, *right* partial inverted chromosome chromosome 11: *left* normal, *right* inverted, chromosome 11, **f** ideograms of chromosomes 9 and 11, inverted chromosomes right of the normal ones

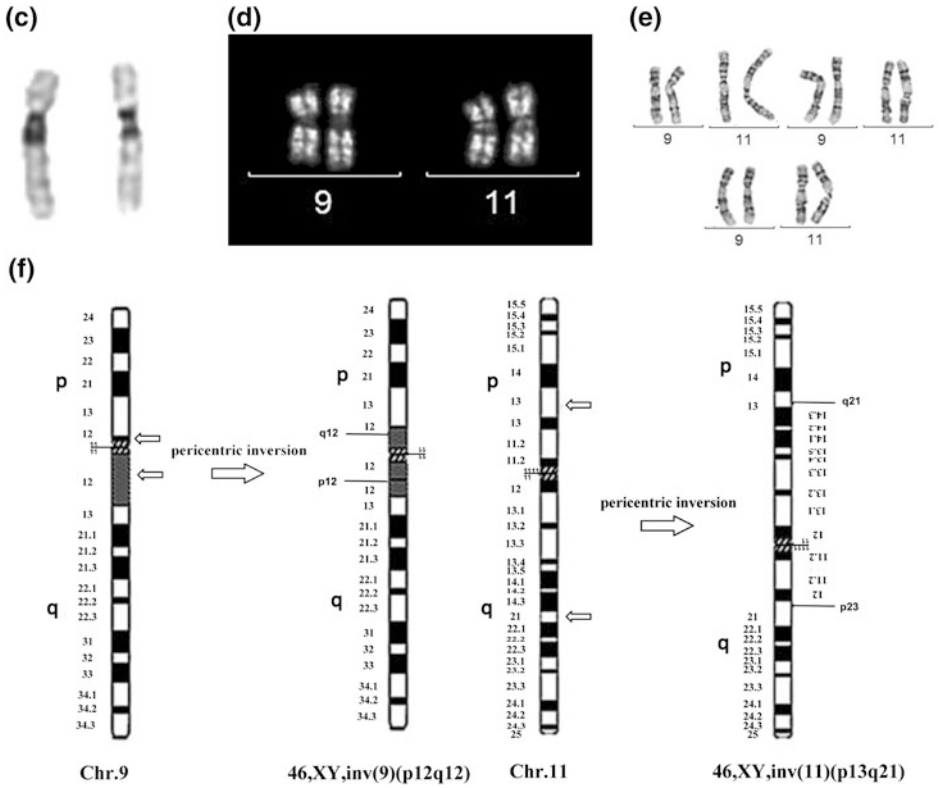

Fig. 4.11 (continued)

Case 12: Karyotype: 46,XX,inv(16)(p13.2q11.1)

Morphology:

The inverted region encloses about 40% of the total length of chromosome 16. The arm ratio has changed from p:q = 40 : 60% to 3 : 97%. The inverted chromosome 16 appears telocentric like the chromosomes 13, 14, 15. In this case CBG banding is of great diagnostic relevance, as only by this technique the position of the centromere and the heterochromatic block q11.2 can be clearly defined.

Cave:

According to our knowledge comparable cases from the literature do not exist. It would be helpful to find as many inversion carriers as possible in the family and to look at pregnancies and offspring of all carriers.

To all carriers prenatal investigations, including microarray, should be recommended. In a pathologic course of pregnancy —abortion, stillbirth—the possible unbalanced karyotype should be analysed and the phenotype of the conceptus documented (Fig. 4.12).

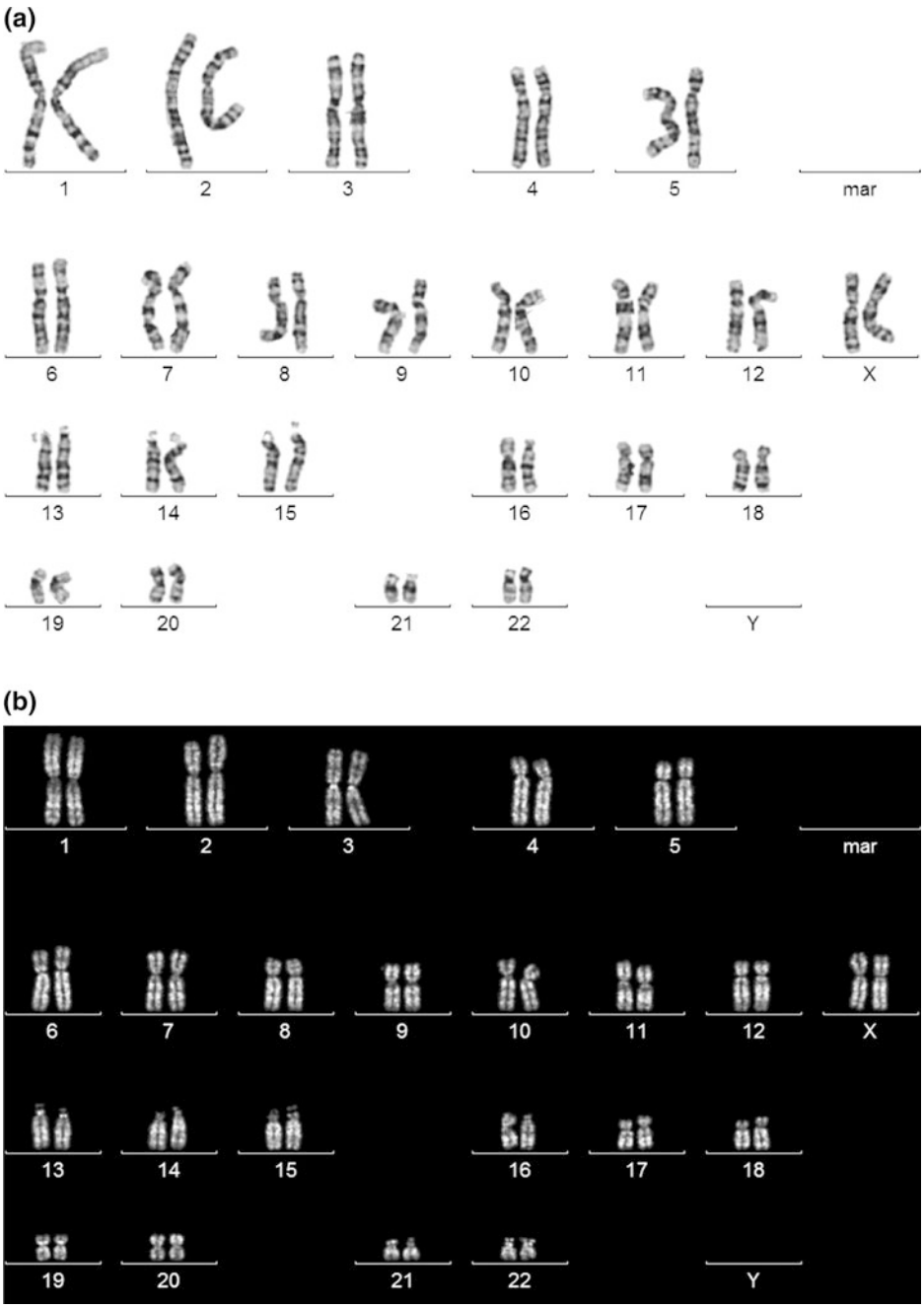

Fig. 4.12 Karyotype 46,XX,inv(16)(p13.2q11.1). **a** GTG-banding, 600 bands per genome, **b** QFQ-banding, 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, **d, e**: *left* normal, *right* inverted chromosome 16, **f** ideograms of case 12, partial dislocation of the centromeric region

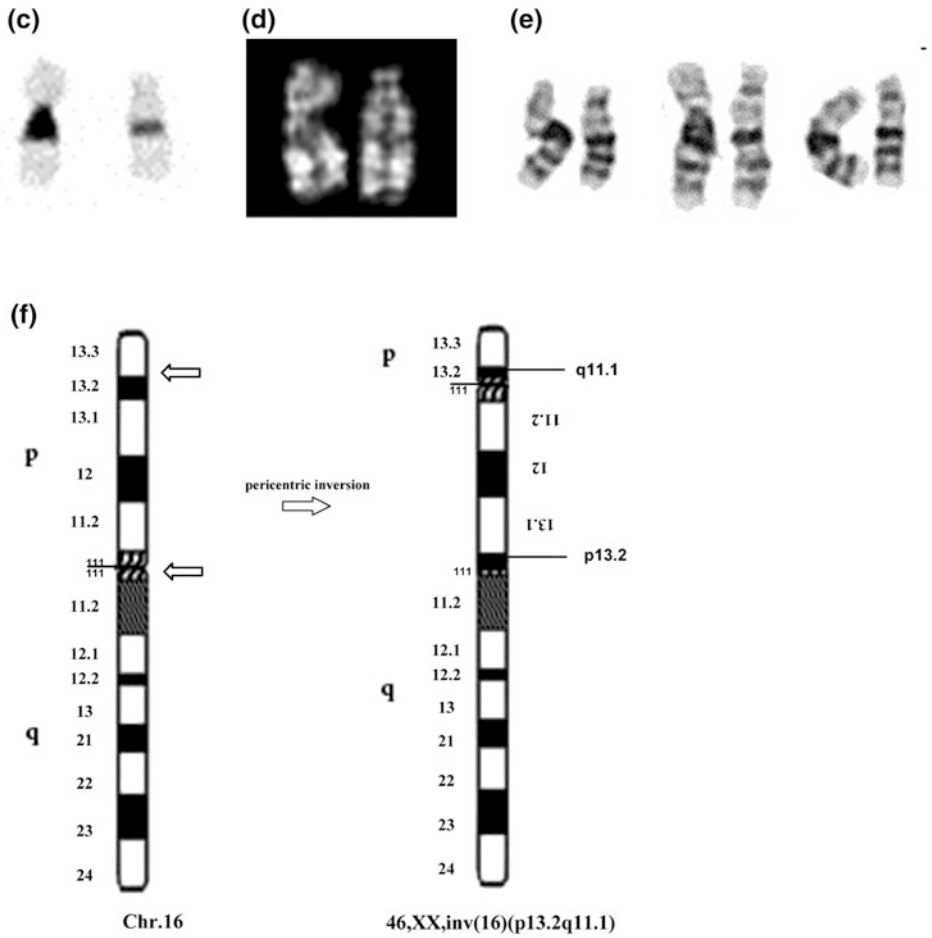

Fig. 4.12 (continued)

Case 13: Karyotype: 46,XY,inv(16)(p12q12.2)
Morphology:

As in the previous case (case 12) the complete heterochromatic block q11.2 has changed its position from the long into the short arm. The inverted region encloses about 40% of the total length of the chromosome, the arm ratio has not changed significantly. Both breakpoints are located in small, AT-rich bands. The altered morphology of the inverted chromosome is characterised by the transposition of the heterochromatic block q11.2 from the long into the short arm. CBG-banding illustrates this change.

Cave:

The risk of meiotic unequal crossing over causing an unbalanced karyotype is given. Therefore genetic counseling and prenatal diagnosis should be offered (Fig. 4.13).

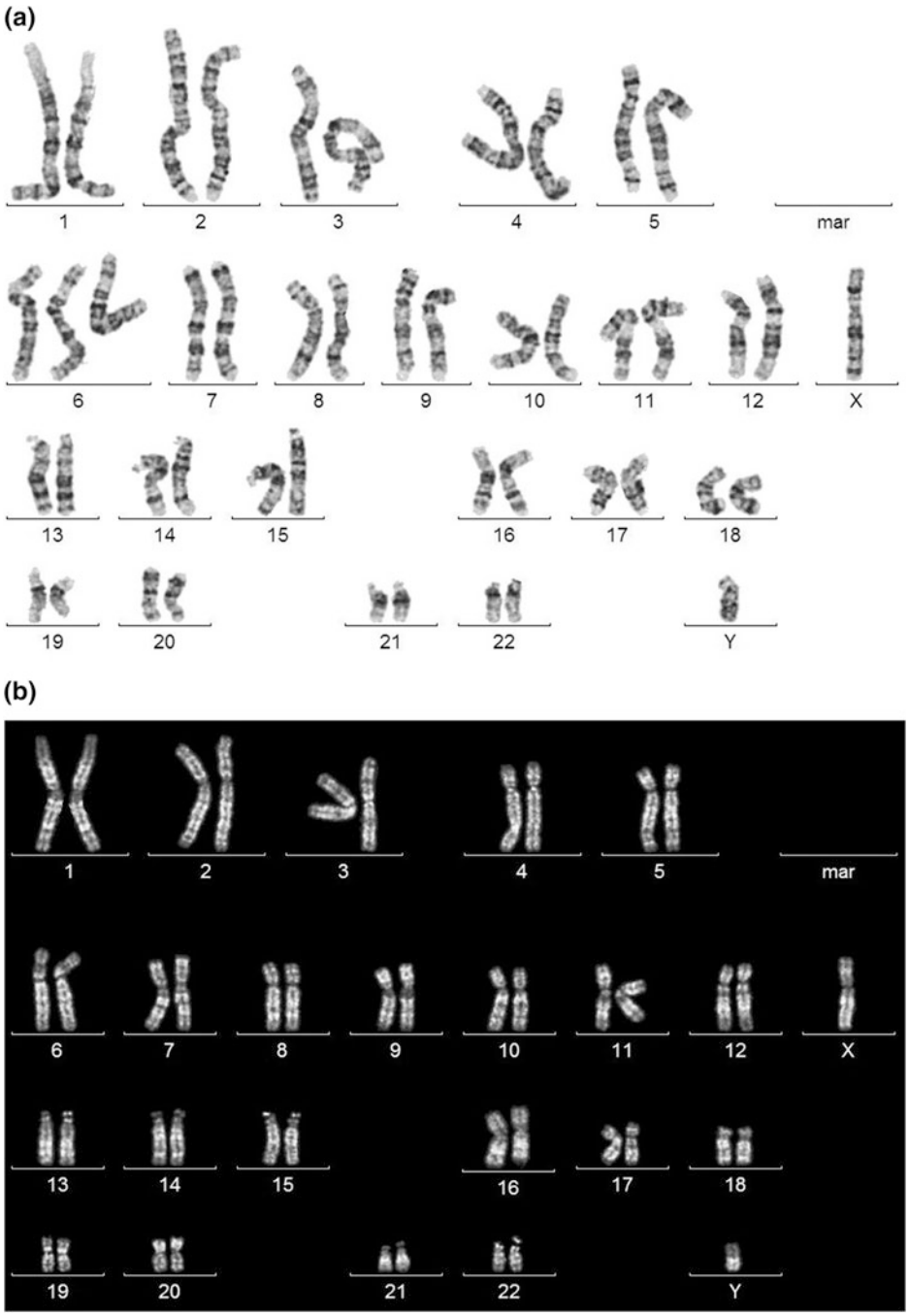

Fig. 4.13 Karyotype 46,XY,inv(16)(p12q12.2). **a** GTG-banding, 700 bands per genome, single pathologic cell with additional chromosome 6, **b** QFQ-banding, 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 16, **e** ideograms of chromosome 16. Transposition of the heterochromatin block into the short arm

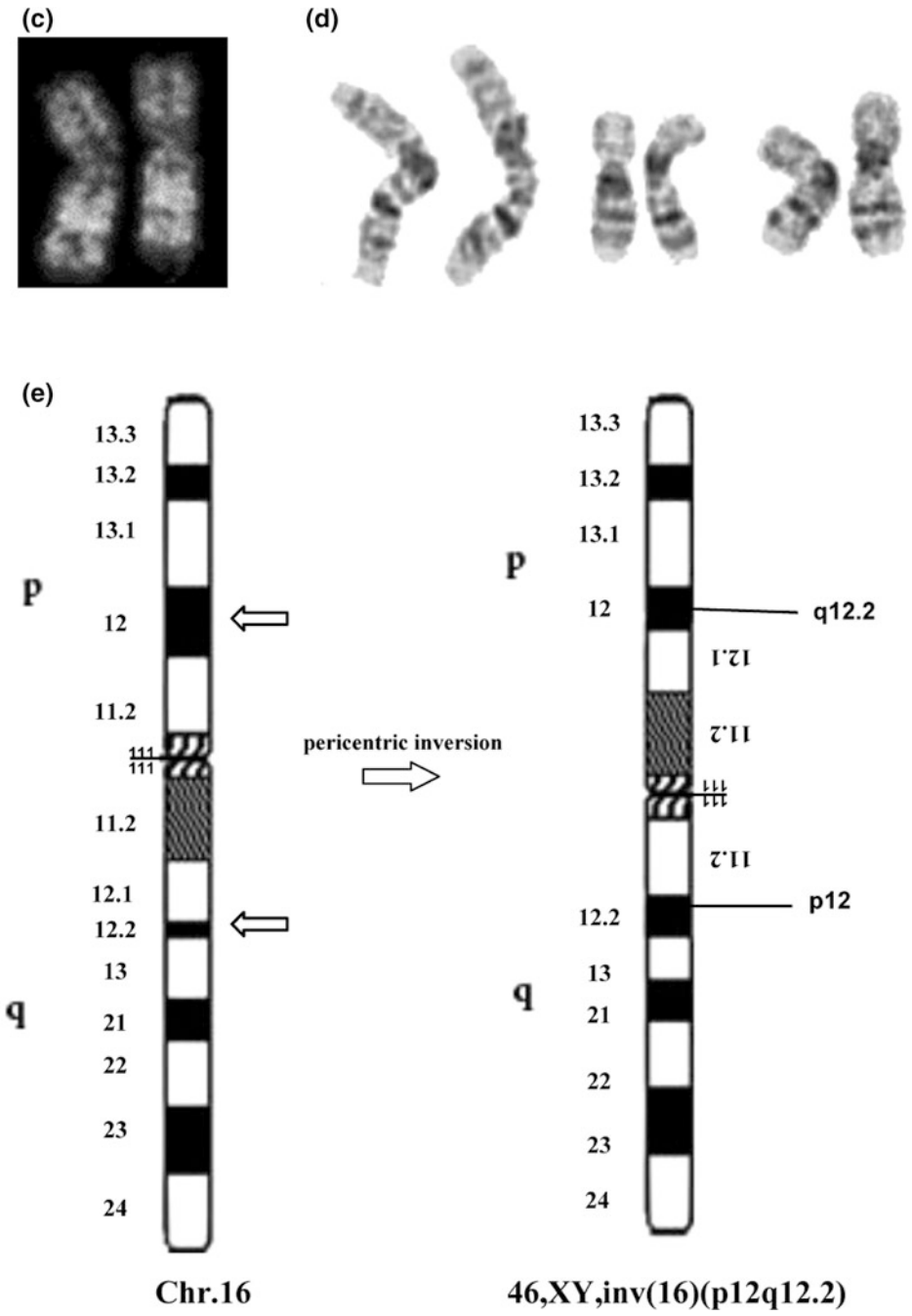

Fig. 4.13 (continued)

Case 14: Karyotype: 46,XX,inv(20)(p13q13.2)
Morphology:

The inverted segment encloses about 70% of the total length of chromosome 20. The inversion product has an altered centromere position and thus appears submetacentric. The main band of the short arm (p12) has been translocated into the proximal region of the long arm. The morphology of the aberrant chromosome shows an altered banding which can be easily recognised even at a resolution of less than 550 bands per genome.

Cave:

This inversion belongs to the group of rearrangements enclosing an inverted region of more than 60% of the total length of the chromosome and is therefore estimated to present with a high genetic risk. Therefore all possible inversion carriers in the family should be investigated. Prenatal diagnoses have to be recommended, including microarray (Fig. 4.14).

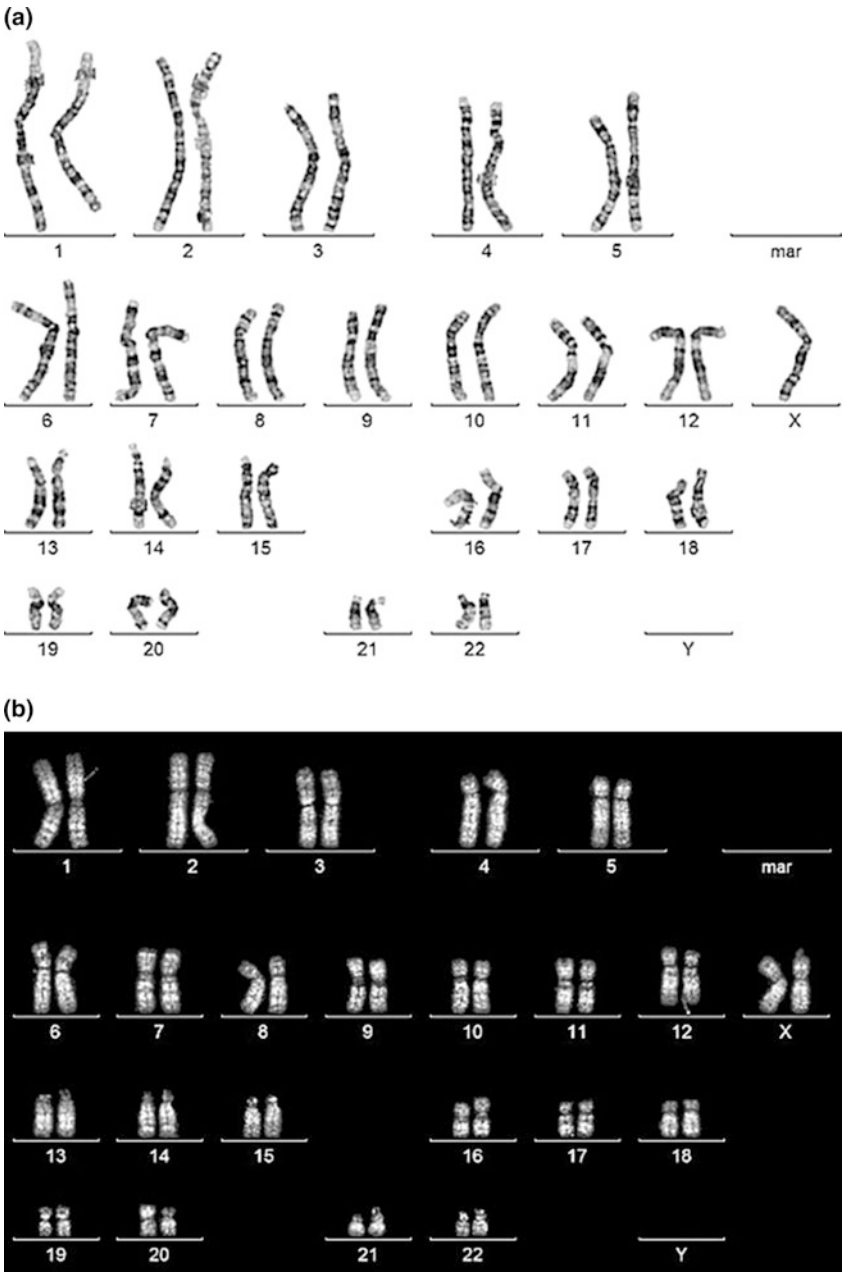

Fig. 4.14 Karyotype 46,XX,inv(20)(p13q13.2). **a** GTG-banding, 1 chromosome X lost by preparation, **b** QFQ-banding, 700 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 20, **d** ideograms of chromosome 20, large inverted segment

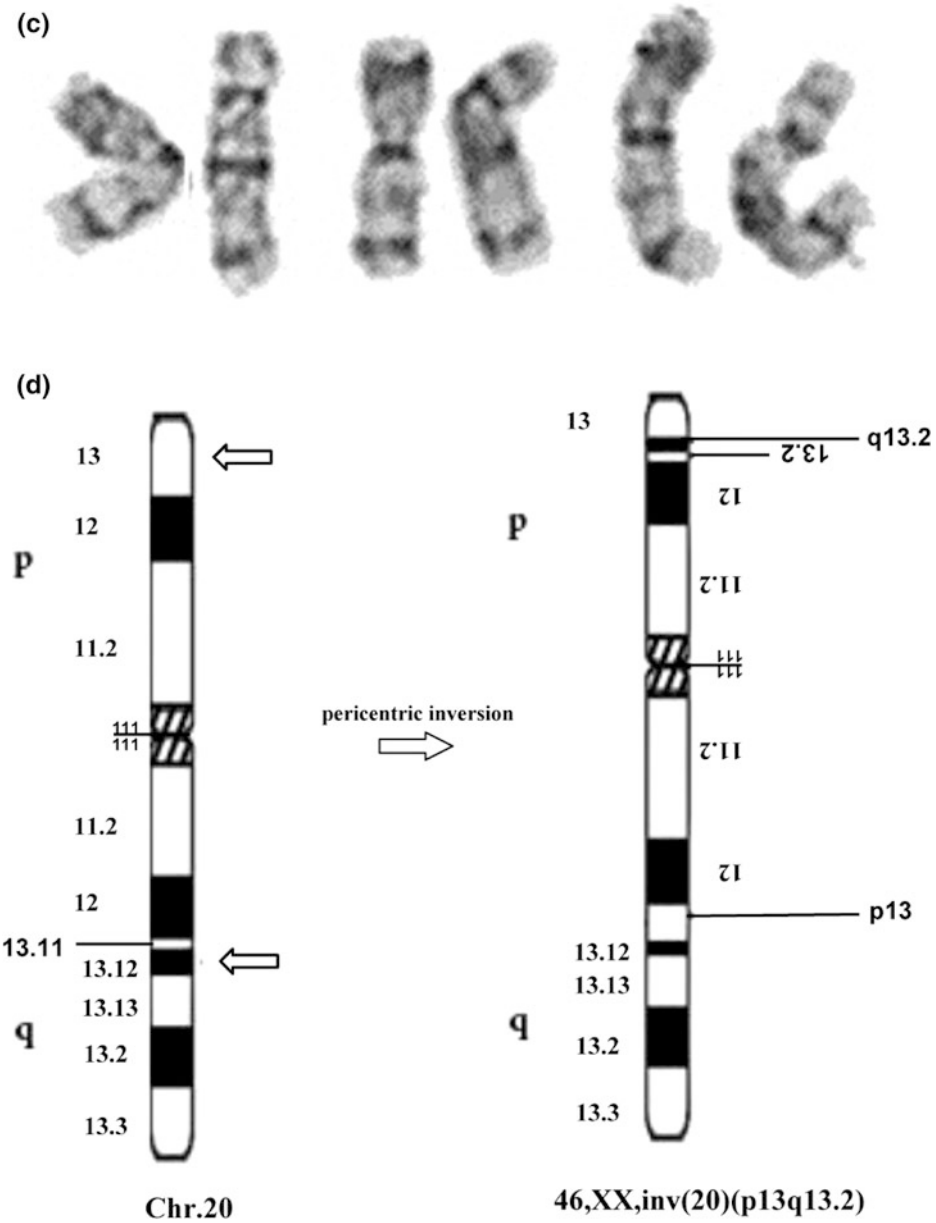

Fig. 4.14 (continued)

Case 15: Karyotype: 46,X,inv(X)(p22.1q26)
Morphology:

The inverted region contains about 80% of the total length of the X-chromosome. The arm ratio changed from about 35:65% to 80:20%. This and the translocation of the AT-rich band q21 into the short arm make the diagnosis quite easy.

Cave:

The risk of an unequal crossing over in meiosis is high because of the size of the inverted segment. The phenotypic alterations will be more severe in males (1 X-chromosome) inheriting an aberrant X-chromosome than in females (2 X-chromosomes). In the latter group the clinical symptoms caused by an unbalanced karyotype can be expected to show great variability caused by a possible screwed inactivation of the second X-chromosome.

An additional risk factor is given when the breakpoint in Xq is localised between q13 and q26 as this can induce primary or secondary amenorrhoea in the female carrier (Fig. 4.15).

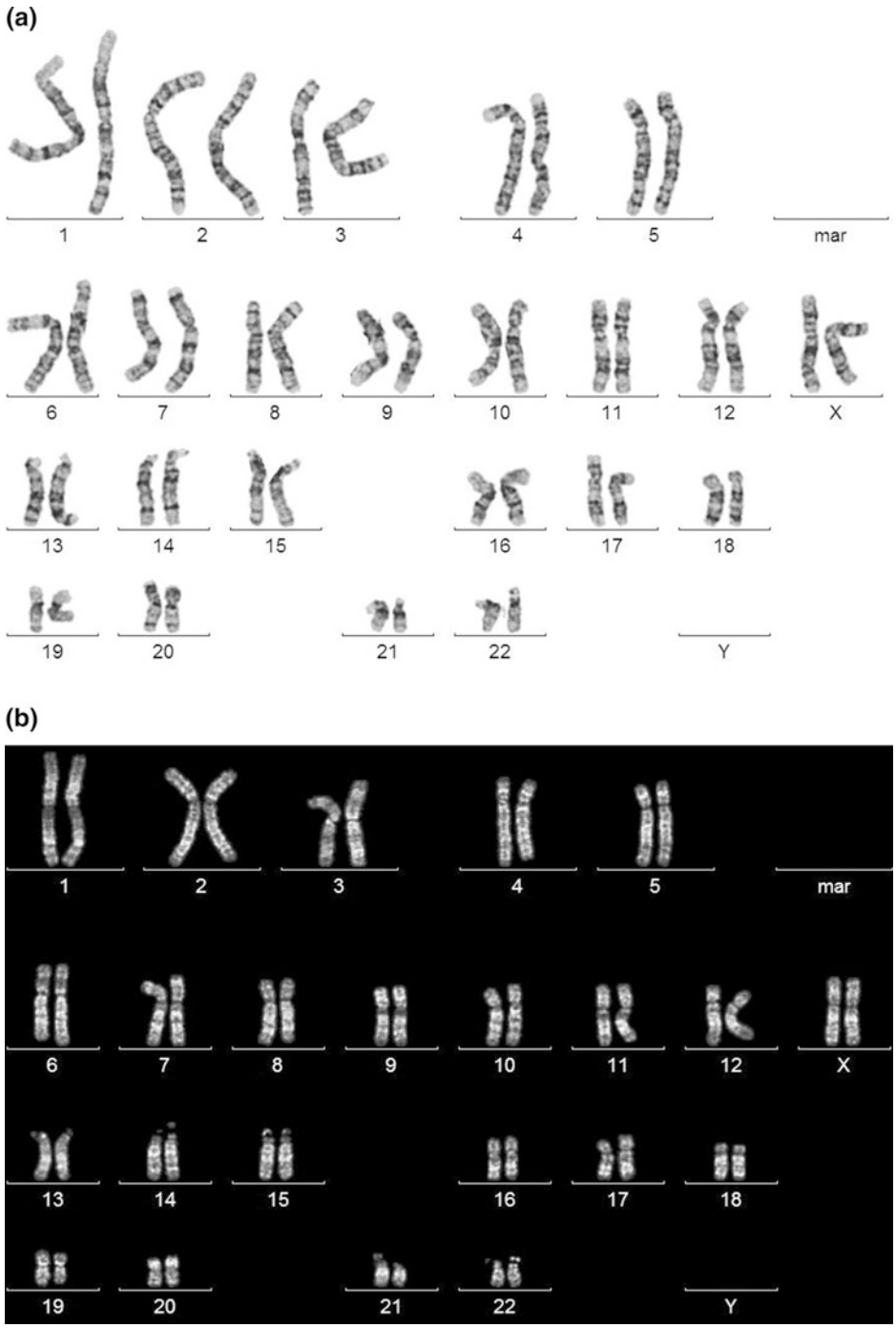

Fig. 4.15 Karyotype 46,X,inv(X)(p22.1q26). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted X-chromosome, **e** ideograms of the X-chromosomes, large inverted segment

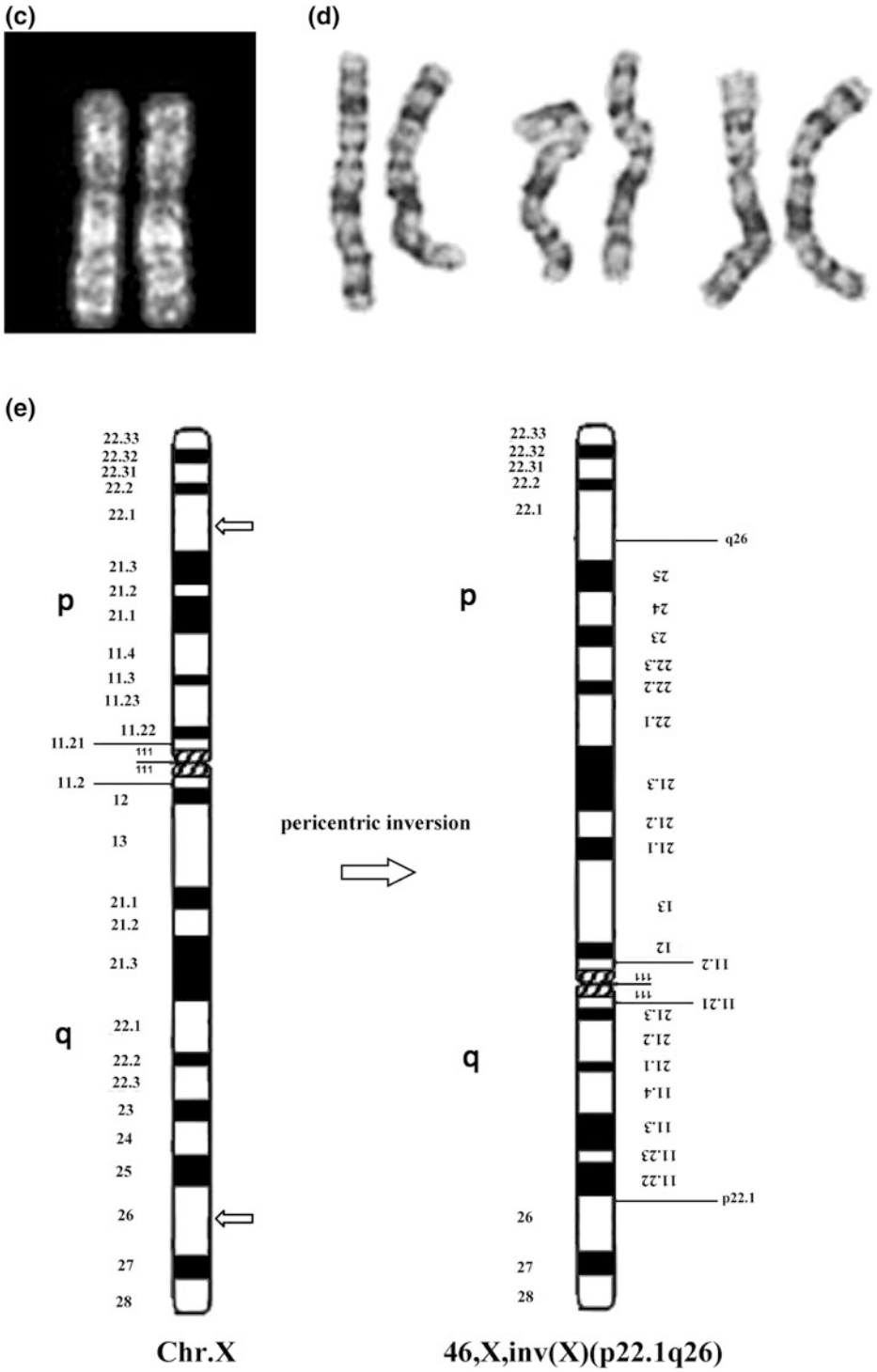

Fig. 4.15 (continued)

Case 16: Karyotype: 46,X,inv(X)(p22.13q24),inv(3)(p11.2q12)

The proband has 2 pericentric inversions: one in the X chromosome with two breakpoints in euchromatic region and one in chromosome 3 which is restricted to the constitutive heterochromatin.

Morphology:

1. inv(3)(p11.2q12)
   The pericentric inversion 3 includes no euchromatic segments and is therefore defined as polymorphism. It can only be diagnosed after QFQ-banding. Its frequency in the European population is about 2% (see: Chap. 2.6).

2. inv(X)(p22.13q24)
   The breakpoints are both located in the distal regions of the short and the long arm. The large inverted segment encloses about 70% of the total length of chromosome X. The arm ratio has changed as in the previous case (case 15) from 35:65% to 55:45% and the aberrant X appears almost metacentric. Besides the altered banding pattern it is characterised by the translocation of the AT-rich bands p22.1 to 22.3 from the short into the long arm and q21.1, q21.3 from the long into the short arm. Therefore the diagnosis is easy to perform.

Cave:

The same genetic risk factors have to be taken into account as in the previous case (case 15) (Fig. 4.16).

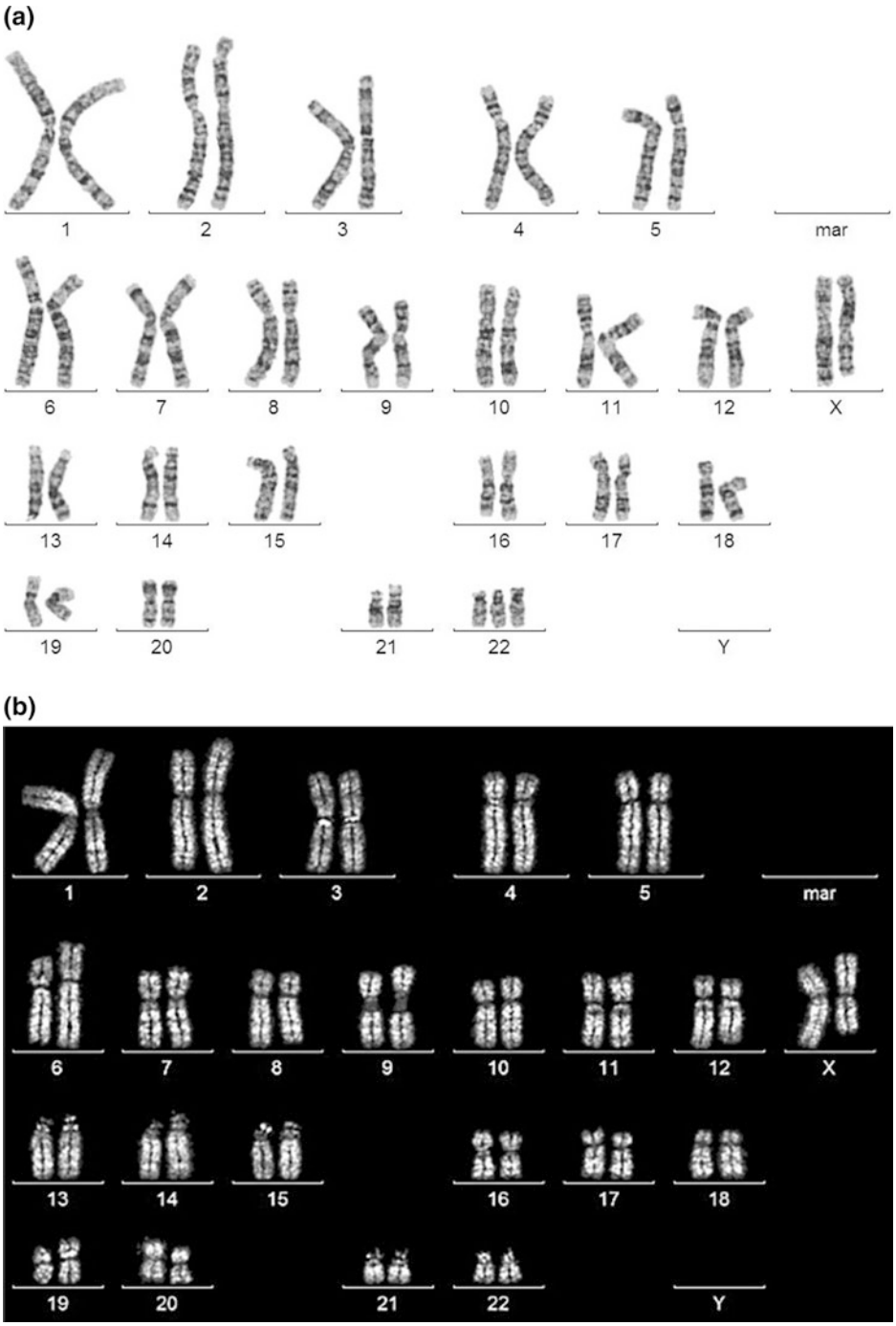

Fig. 4.16 Karyotype 46,X,inv(X)(p22.13q24),inv(3)(p11.2q12). **a** GTG-banding, single pathologic cell with additional chromosome 22, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, d: GTG-banding, chromosome 3 and X from different mitoses, *left* normal, *right* inverted chromosomes, **e**, **f** normal and inverted ideograms of chromosome 3 and X

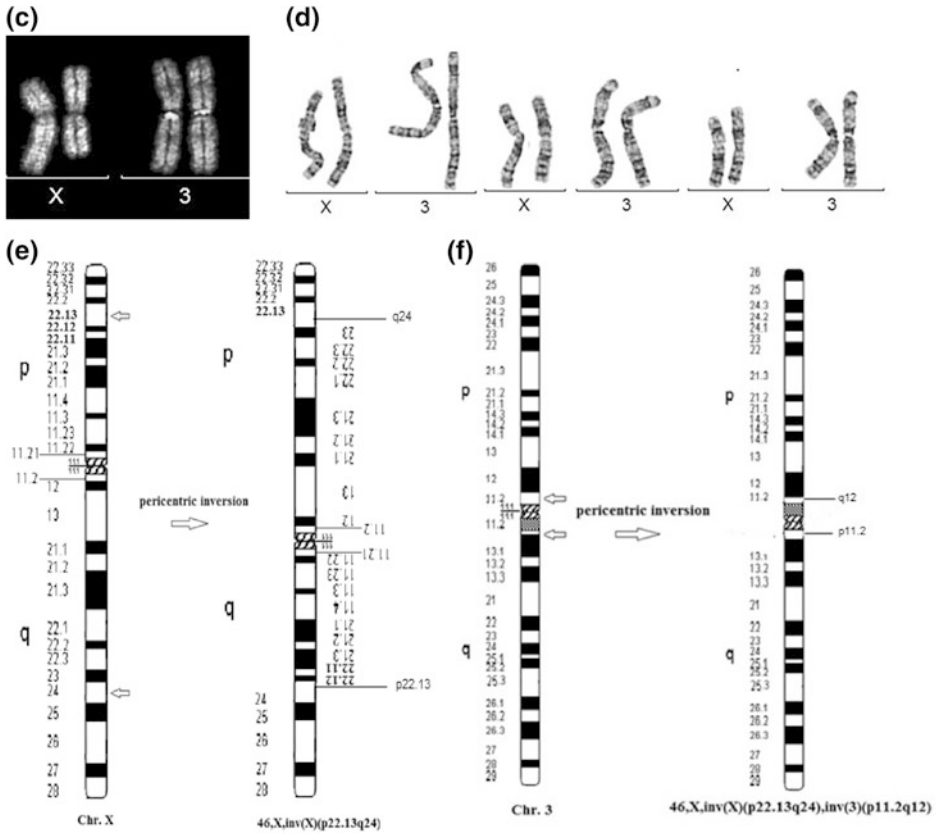

Fig. 4.16 (continued)

Case 17: Karyotype: 46,X,inv(Y)(p11.2q11.23)
Morphology:

The pericentric inversion presented here demonstrates a complete transfer of the distal heterochromatic band q12 from the long into the short arm. The aberrant chromosome is metacentric. In this case the inverted region incloses about 50% of the total length of the Y-chromosome. Caused by the variation in length of q12 in different probands this index can only be determined for the individual carrier. The specific presentation of the inverted chromosome should be done not only by QFQ but also by DA/DAPI-banding as the proximal heterochromatic region of Yq12 can only be analysed by DA/DAPI. This is of diagnostic relevance, because a breakpoint in the proximal heterochromatin is of no genetic importance in contrast to a breakpoint in the following euchromatin.

Cave:

The Y-inversion presented here has a frequency of 1–2‰ with differences in single ethnic groups. There is a large variability in phenotypic peculiarities caused by possible pairing abnormalities of X and Y that can lead to oligo- and azoospermia in the carrier (Fig. 4.17).

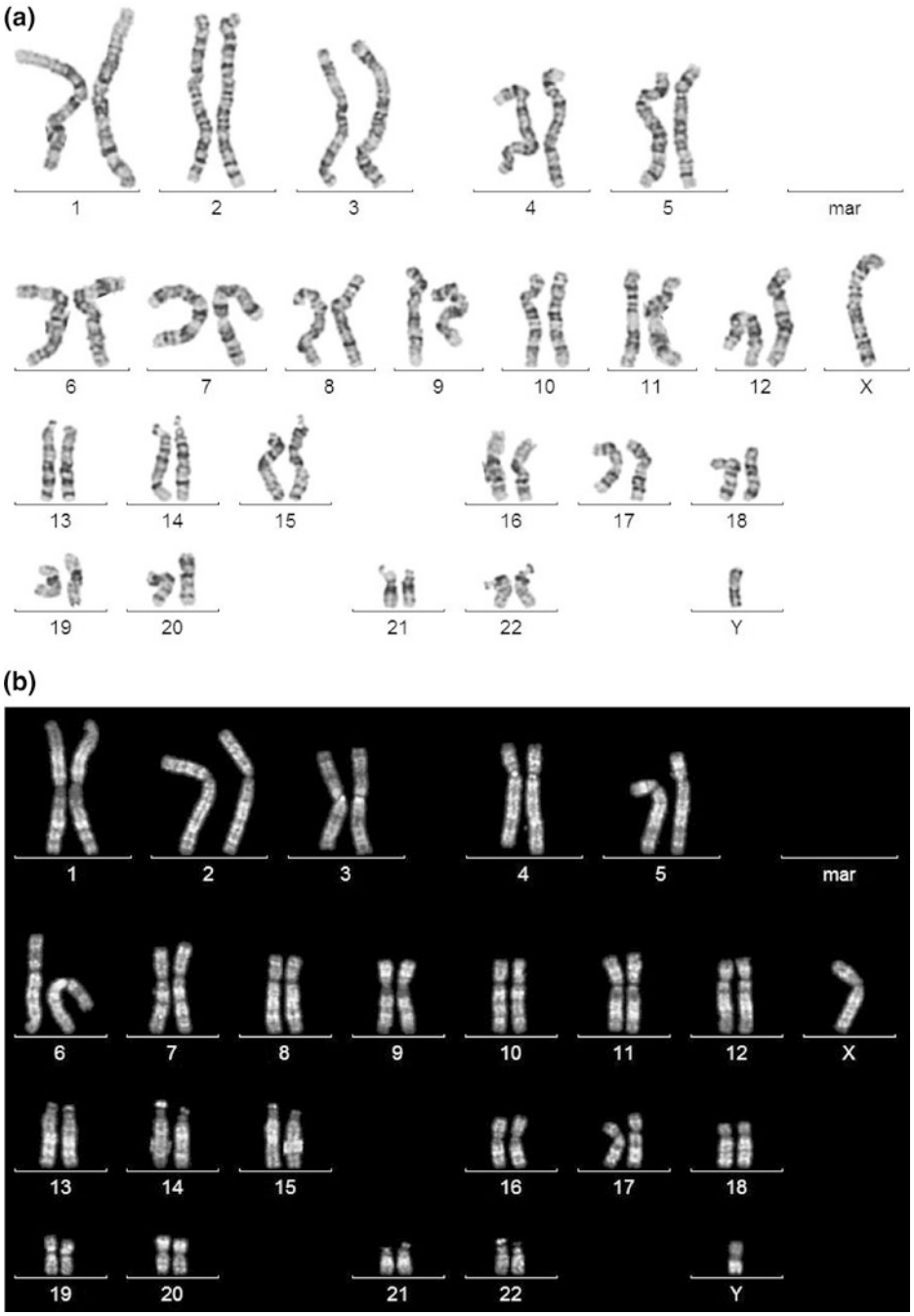

Fig. 4.17 Karyotype 46,X,inv(Y)(p11.2q11.23). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, Y-chromosome from different mitoses, d/1: Y-chromosome from a normal control person, **f** ideograms of Y-chromosome, the inverted segment leads to a metacentric morphology

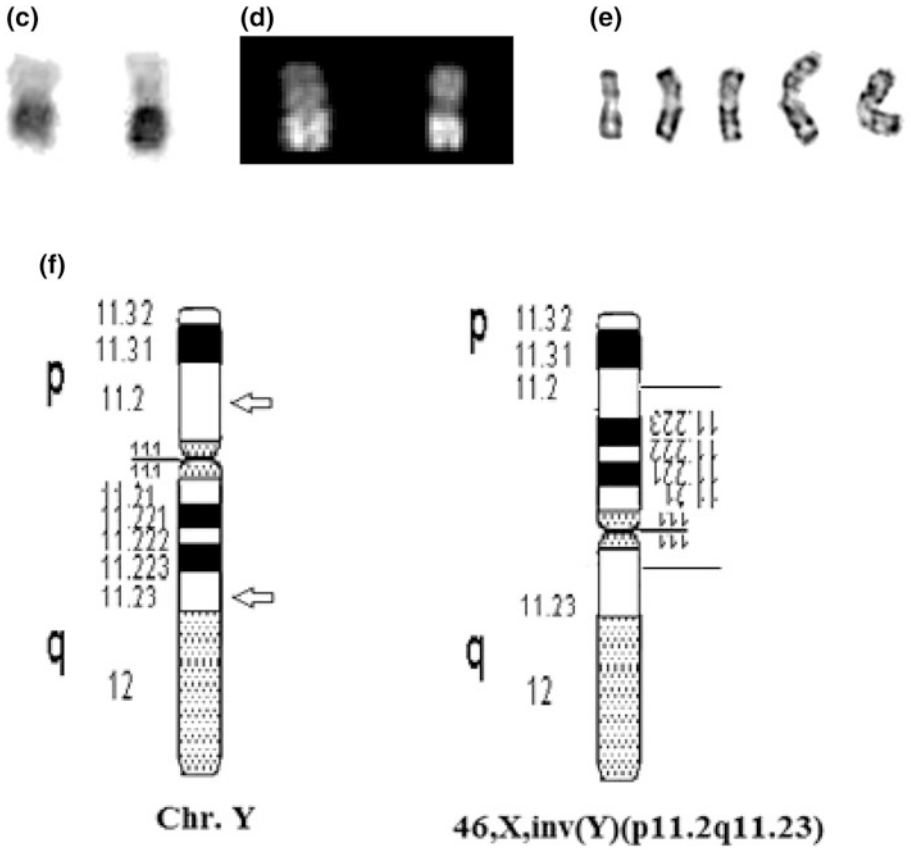

Fig. 4.17 (continued)

Paracentric Inversions

18 46,XY,inv(1)(p32.1p36.1)
19 46,XY,inv(1)(q11.1q24.2)
20 46,XX,inv(2)(q14.2q21.1)
21 46,XY,inv(3)(p22.2p25)
22 46,XY,inv(4)(q13.2q27–q28.2)
23 46,XY,inv(5)(p11p15.1)
24 46,XX,inv(6)(q16.2q24.2)
25 46,XY,inv(6)(q23.3q25.3)
26 46,XX,inv(6)(q25.1q25.3)
27 46,XX,inv(7)(p14.2p21.2)
28 46,XY,inv(8)(q13q24.22)
29 46,XY,inv(9)(q32q34.3)
30 46,XX,inv(11)(q21q23.3)
31 46,XX,inv(12)(q21.1q24.1)
32 46,XX,inv(13)(q12.1q22)
33 46,XY,inv(13)(q13q32)
34 46,XX,inv(13)(q21.2q31)
35 46,XX,inv(14)(q23.3q32.2),inv(3)(p11.2q12)(x2)
36 46,XX,inv(15)(q24q26.3)
37 46,XY,inv(19)(p12p13.13)
38 46,XX,inv(19)(q13.31q13.42)
39 46,X,inv(X)(p11.3p22.32)
40 46,X,inv(Y)(q11.21q12),inv(9)(p12q12),inv(9)(p12q13)

Case 18: Karyotype: 46,XY,inv(1)(p32.1p36.1)

Morphology:

The case presented here shows a small distal inversion in the short arm (p) which comprises only about 10–15% of the total length of chromosome 1. This inversion is in spite of its small extend easy to identify because of the shift of AT-rich bands into the distal GC-rich segment. A further peculiarity of the inverted chromosome is the division of the heterochromatic block q12 into 3 subunits. This is a polymorphism without genetic relevance (see: Chap. 2.6).

Cave:

The region 1p36 contains an aberration hot spot. If a microdeletion (del < 5 Mb) occurs in this locus the carrier shows a characteristic severe malformation syndrome. On the basis of this observation all carriers of the aberration type presented here should be recommended prenatal diagnosis in each pregnancy because of the risk of an unequal crossing over in meiosis, and this investigation has to include microarray or FISH (LSI-probes) analyses. Relatives of the carrier should be recommended to perform chromosome analyses (Fig. 4.18).

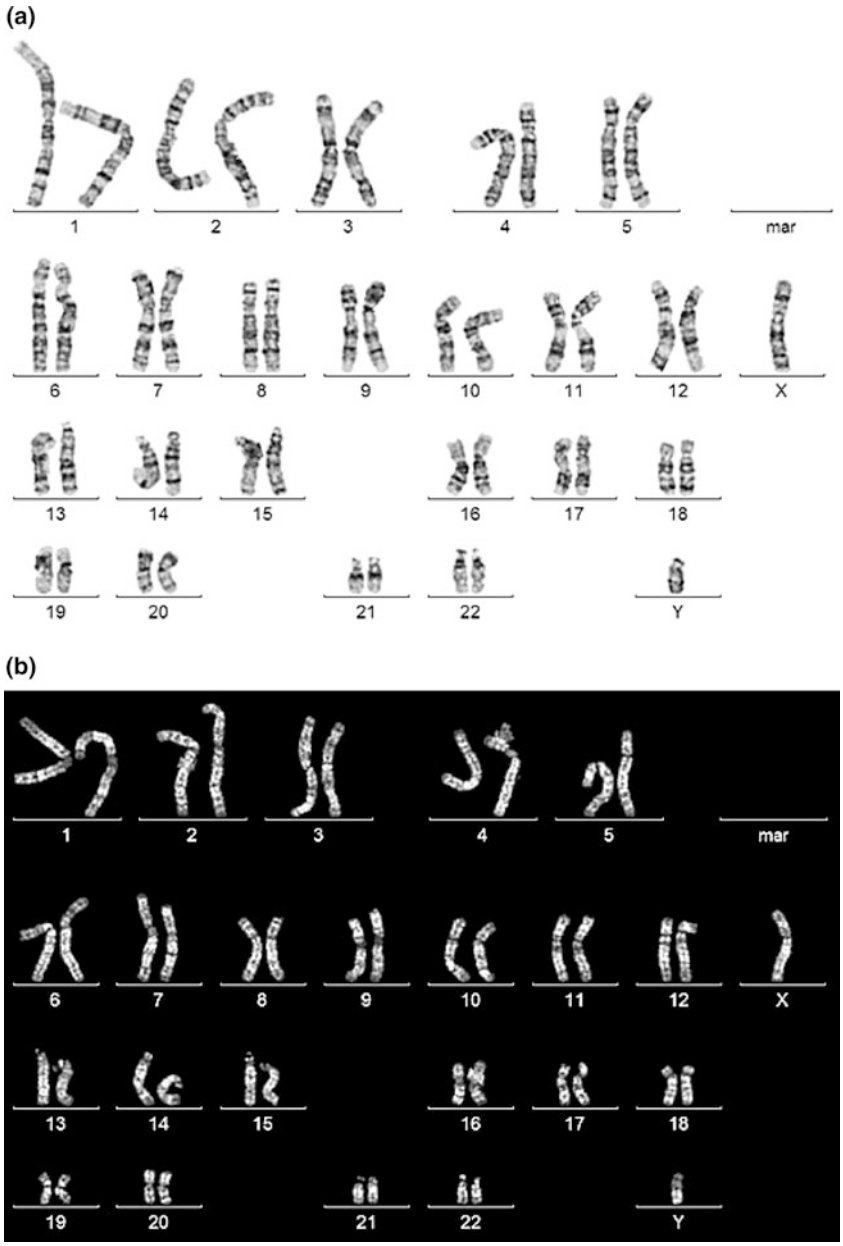

Fig. 4.18 Karyotype 46,XY,inv(1)(p32.1p36.1). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 1, **e** ideograms of chromosome 1, small inverted segment in the short arm

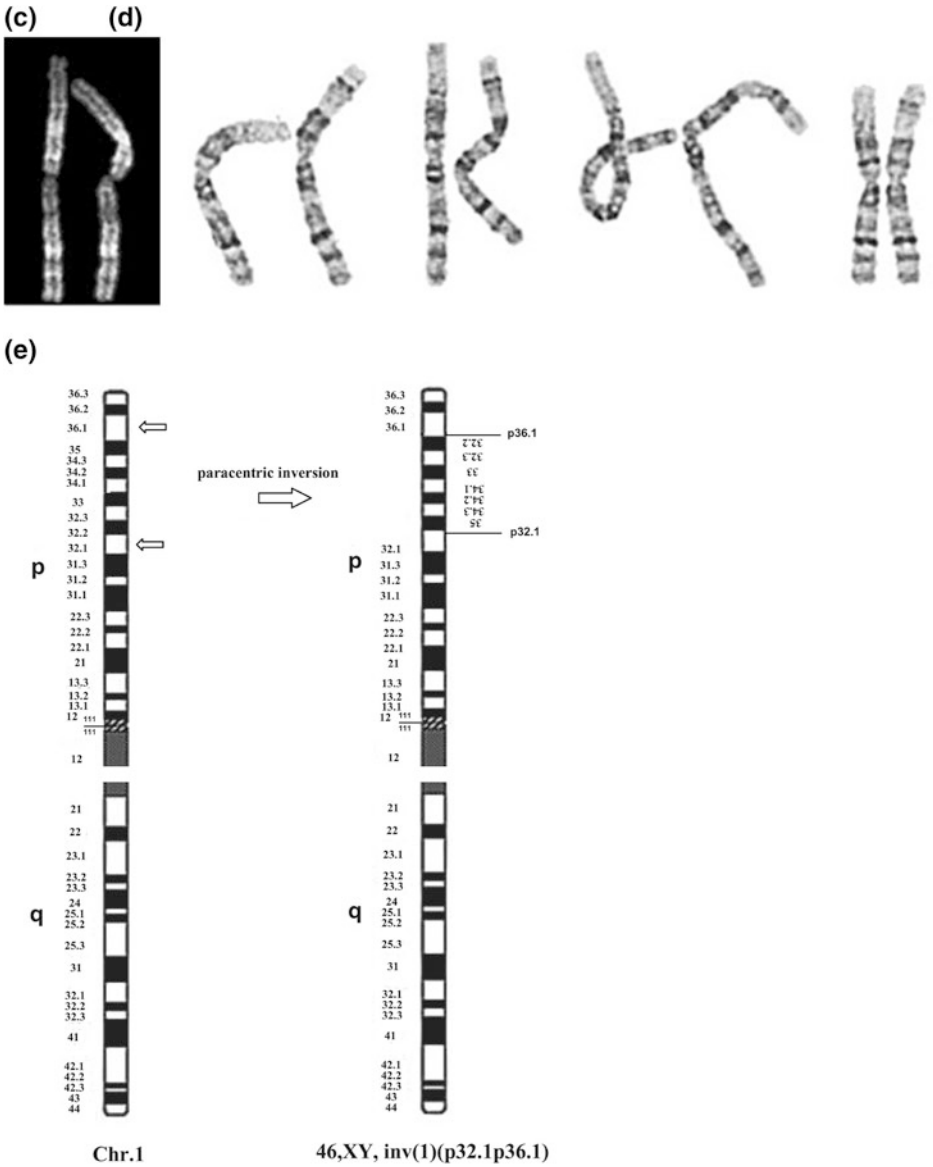

Fig. 4.18 (continued)

Case 19: Karyotype: 46,XY,inv(1)(q11.1q24.2)

Morphology:

The inverted segment includes about 50% of the long arm (q) of chromosome 1. Its size corresponds to almost 22% of the length of this chromosome. The proximal breakpoint is located in the peripheral region of the centromere (q11.1) and therefore in a non-coding segment. The phenotype of the inverted chromosome is especially characterised by the dislocation of the heterochromatic block q12 from its pericentromeric position into the intermediate band q24.2. In this case CBG-banding gives the best presentation of the rearranged heterochromatic block.

Cave:

The case presented here is a rare type of inversion. Therefore the genetic risk caused by an unequal meiotic crossing over is not easy to check. Thus, in the course of genetic counseling of the carrier and his family potential inversion carriers should be investigated and prenatal analyses should be recommended to all of them (Fig. 4.19).

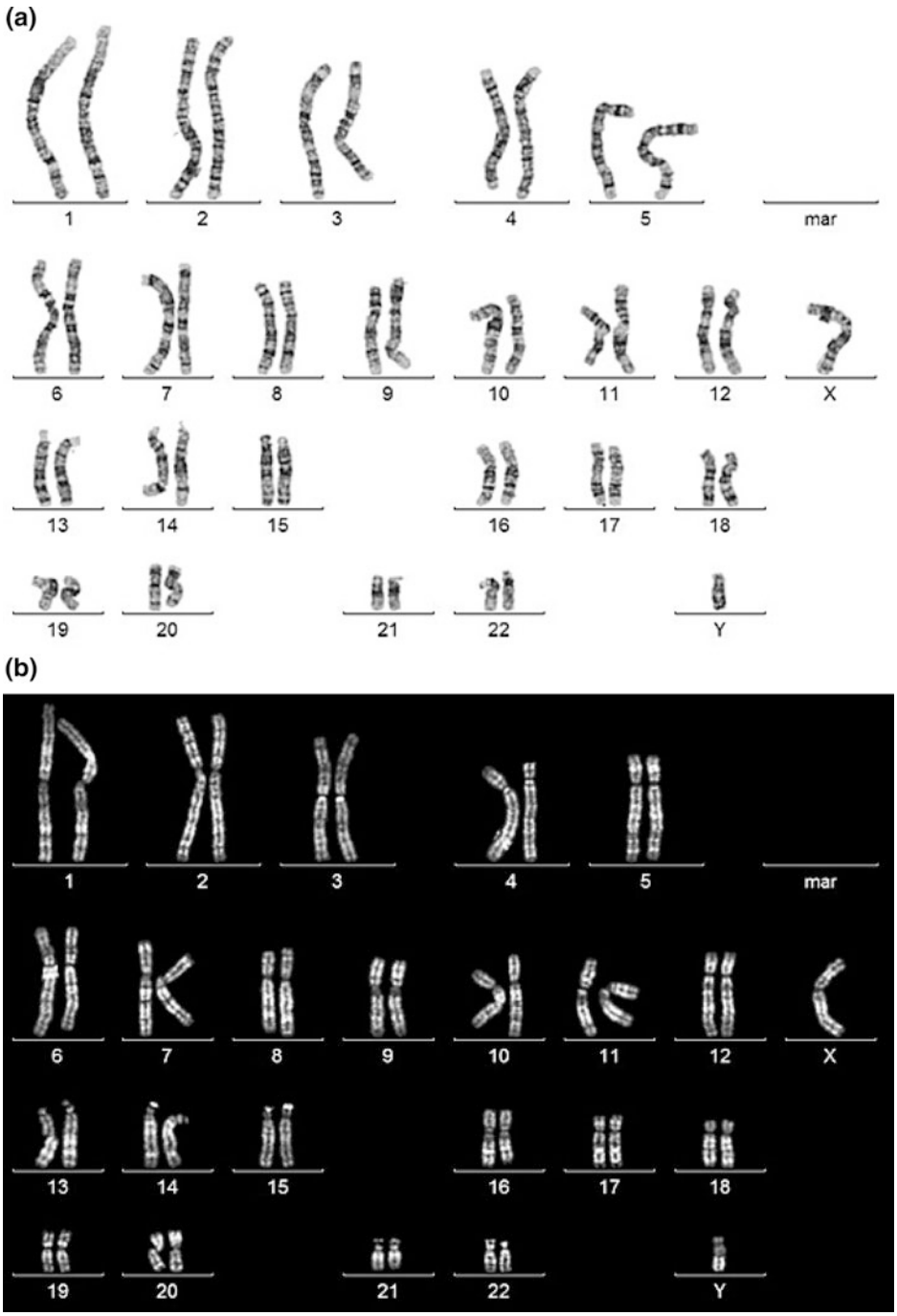

Fig. 4.19 Karyotype 46,XY,inv(1)(q11.1q24.2). **a** GTG-, **b** QFQ-banding, 700 and 550 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 1, **f** ideograms of chromosome 1. Characteristic changed appearance by dislocation of the heterochromatic block

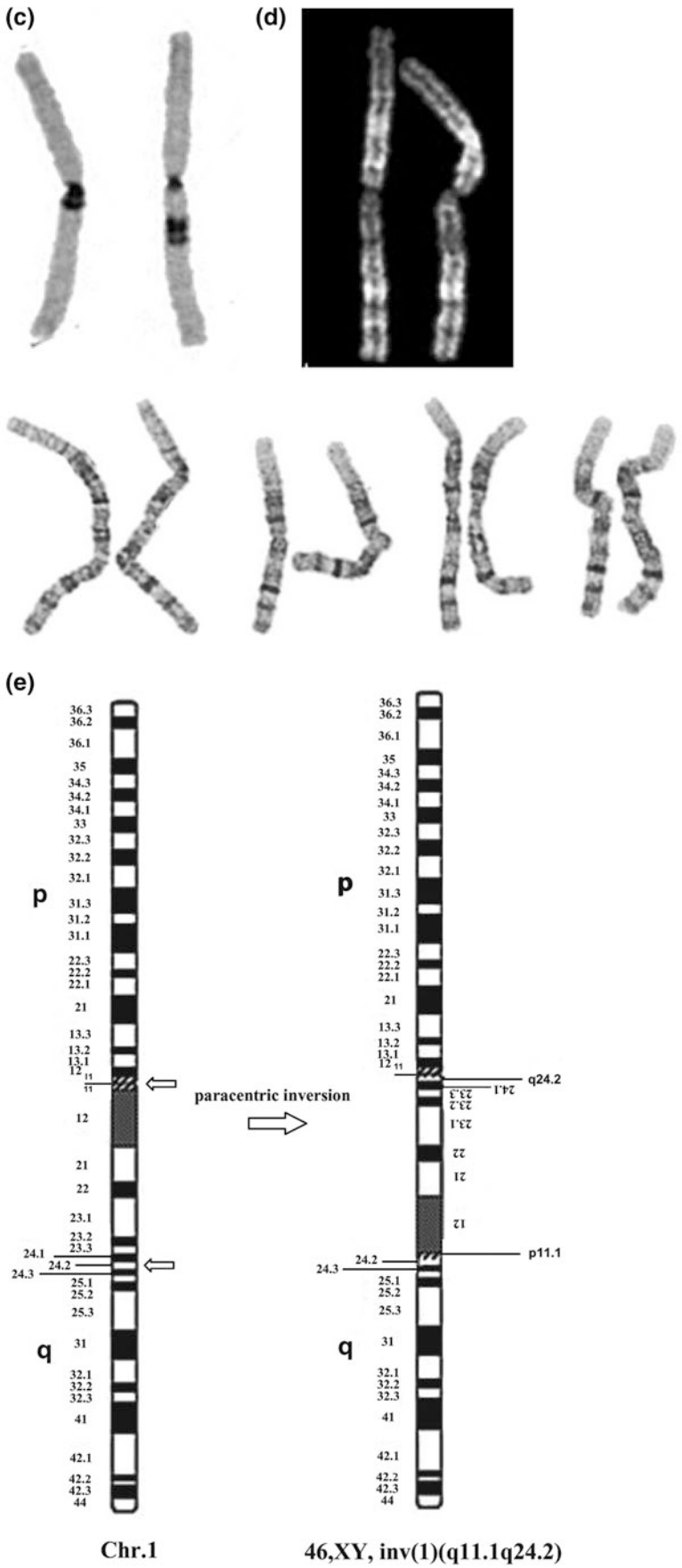

Fig. 4.19 (continued)

Case 20: Karyotype: 46,XX,inv(2)(q14.2q21.1)
Morphology:

The small paracentric inversion located in the intermediate region of the long arm, comprises only about 4% of the total length of chromosome 2. The identification of this inversion requires a high banding resolution of 700–850 bands, as can be delineated from the GTG karyotype.

Cave:

As in the previous cases genetic counseling and prenatal diagnoses are indicated (Fig. 4.20).

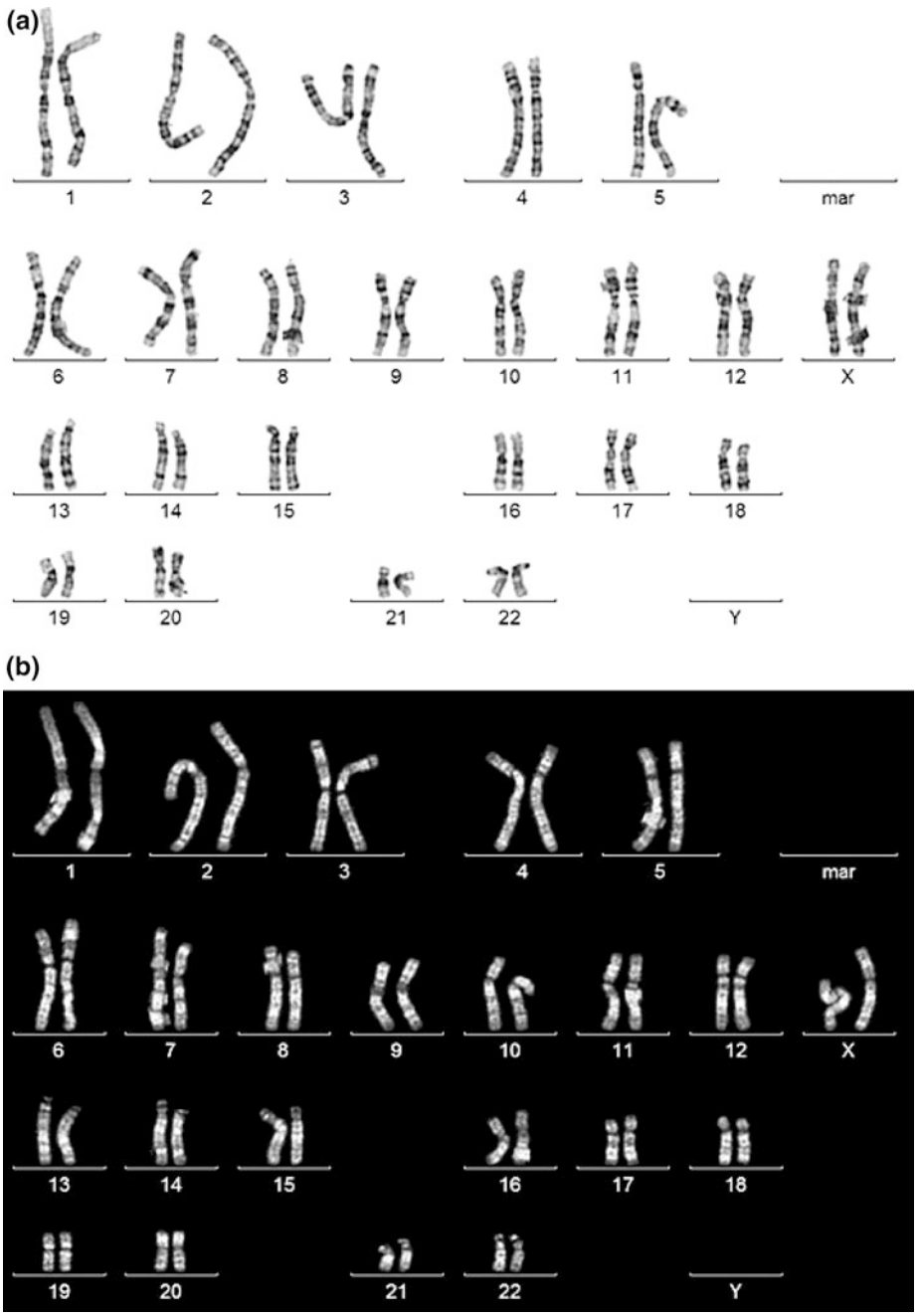

Fig. 4.20 Karyotype 46,XX,inv(2)(q14.2q21.1). **a** GTG-, **b** QFQ-banding, 700 and 550 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 2, **e** ideograms of chromosome 2, small inverted segment in the proximal long arm

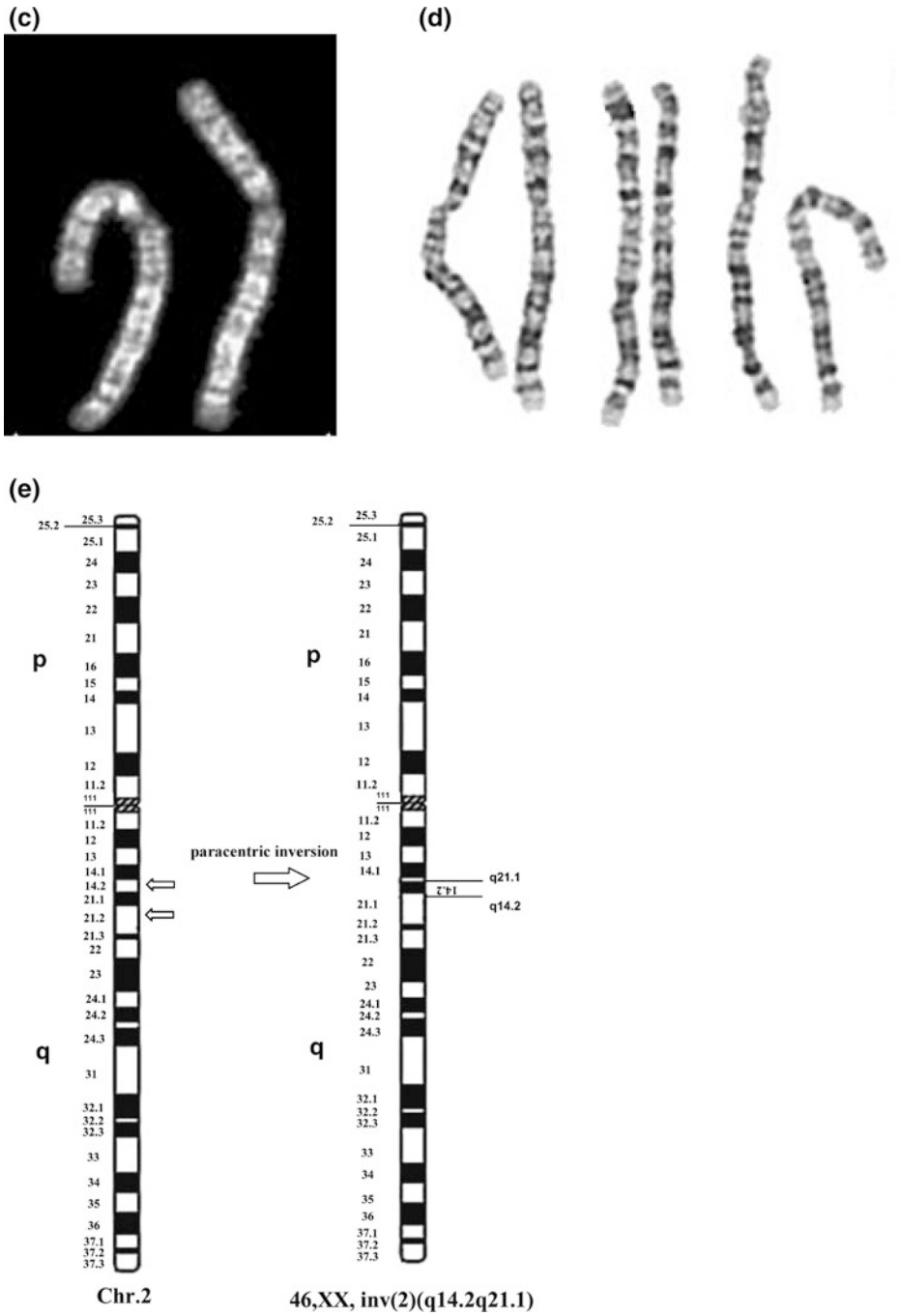

Fig. 4.20 (continued)

Case 21: Karyotype: 46,XY,inv(3)(p22.2p25)
Morphology:

The inverted segment is located in the distal part of the short arm of chromosome 3. The length of the inversion is about 12% of the total length of chromosome 3. The exact localisation of the breakpoints is only possible at a resolution of 550–700 bands per genome. Among the paracentric inversions chromosome 3 is frequently involved and the locus p25 is a common breakpoint.

Cave:

The genetic risk is estimated to be low, but precise figures can't be given because of the small number of cases published until now (Fig. 4.21).

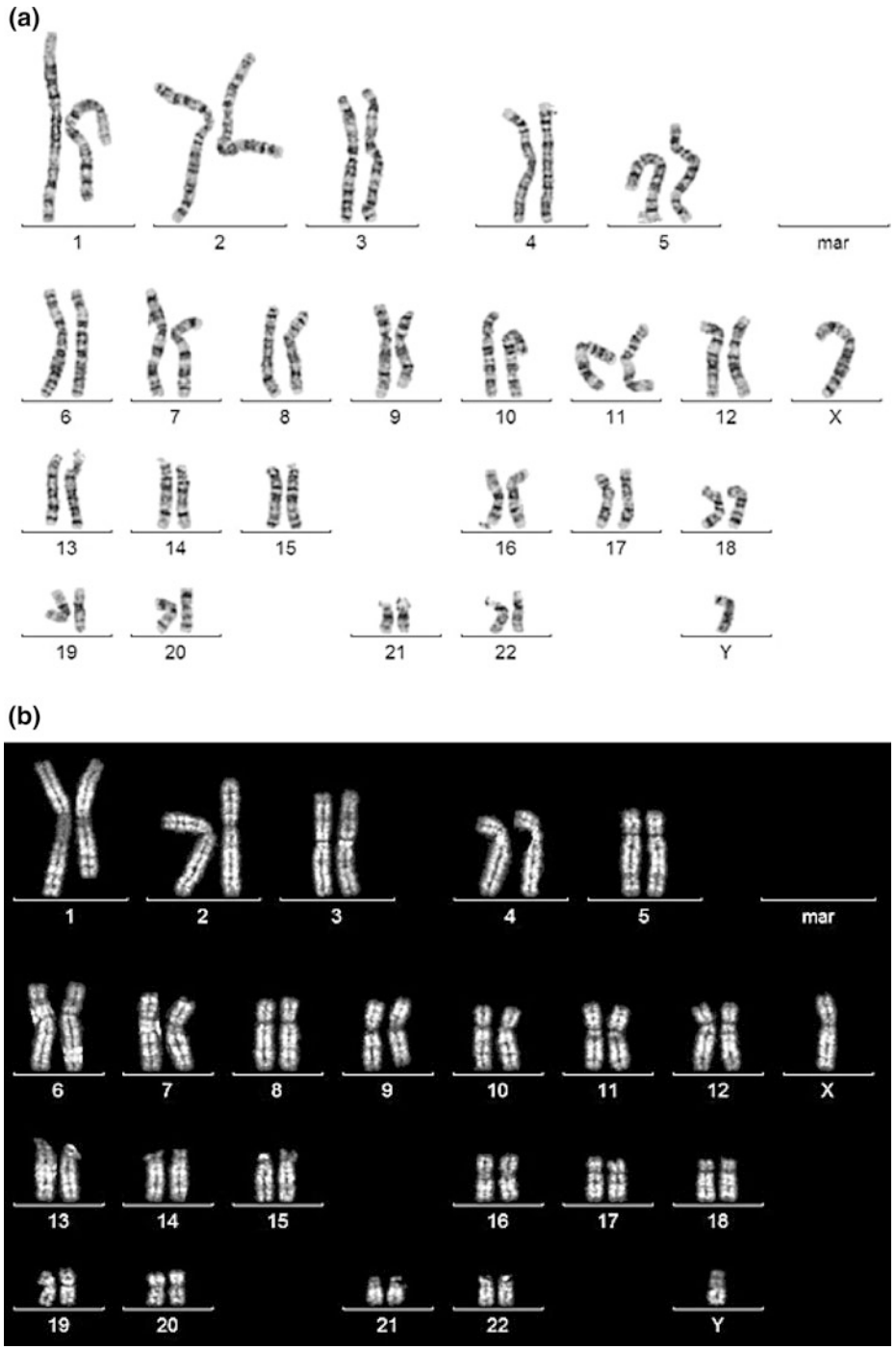

Fig. 4.21 Karyotype 46,XY,inv(3)(p22.2p25). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 3, **e** ideograms of chromosome 3, small, distal segment inverted in the short arm

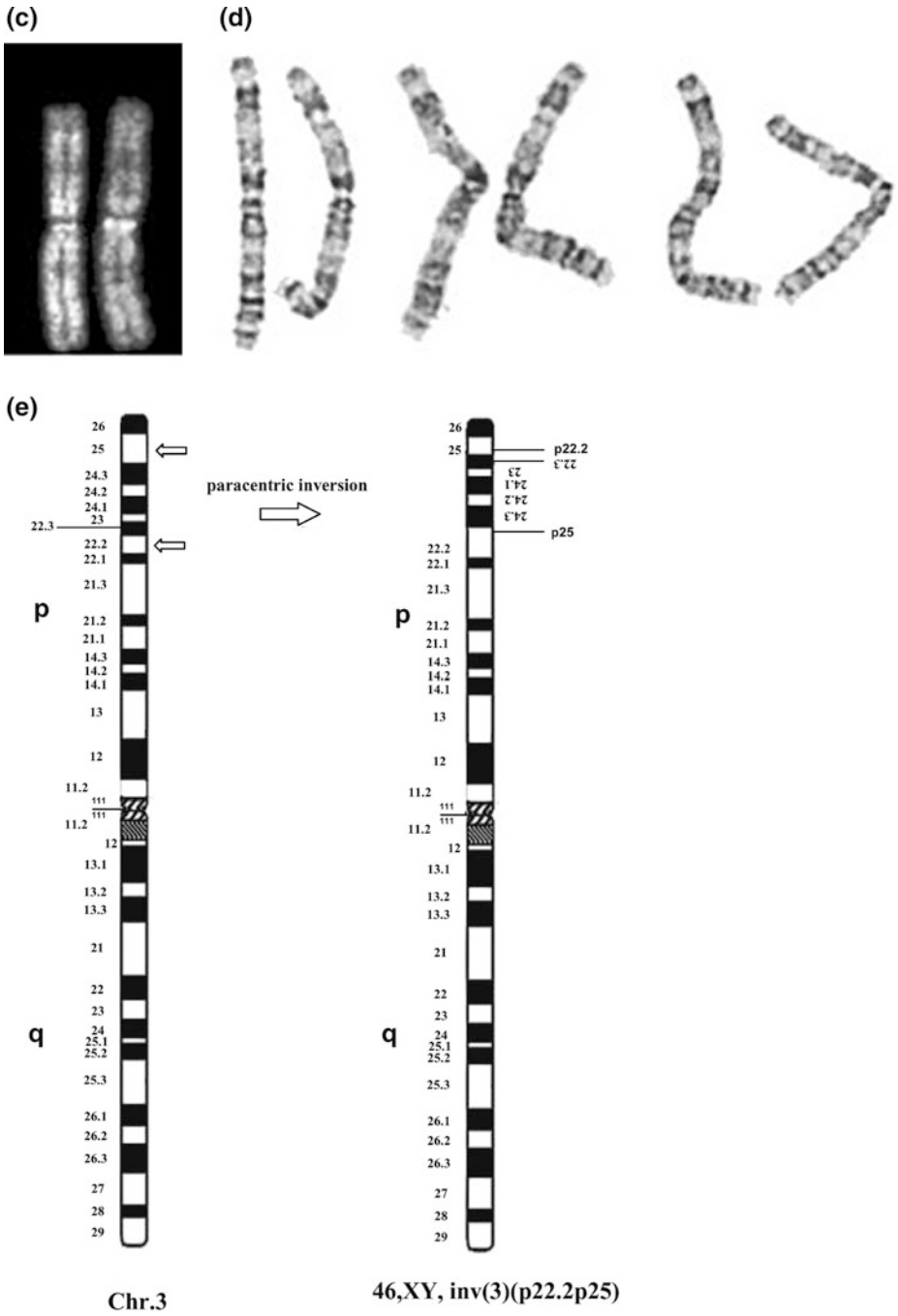

Fig. 4.21 (continued)

Case 22: Karyotype: 46,XY,inv(4)(q13.2q27–q28.2)
Morphology:

The paracentric inversion in the long arm (q) of chromosome 4 comprises about 30% of its total length. The analysis of the rearrangement is primary performed by the verification of the dislocation of the distal band (q13.2) part of the AT-rich double band q13. For successful diagnosis a resolution of 550–700 bands per genome has to be recommended.

Cave:

No specific additional risk factors are documented besides those of a paracentric inversion of the given size (Fig. 4.22).

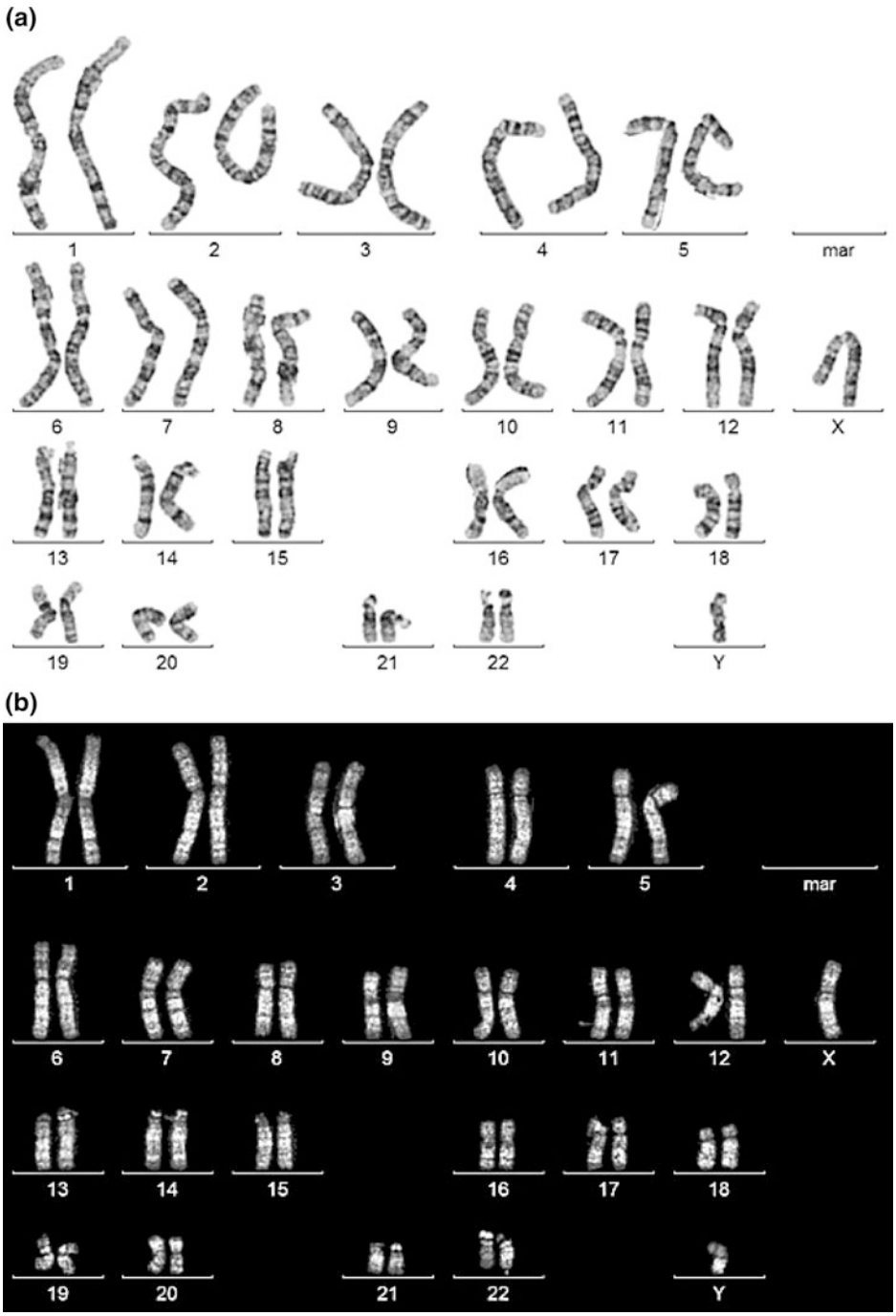

Fig. 4.22 Karyotype 46,XY,inv(4)(q13.2q27–q28.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 4, **d** ideograms of chromosome 4, inverted segment in the long arm

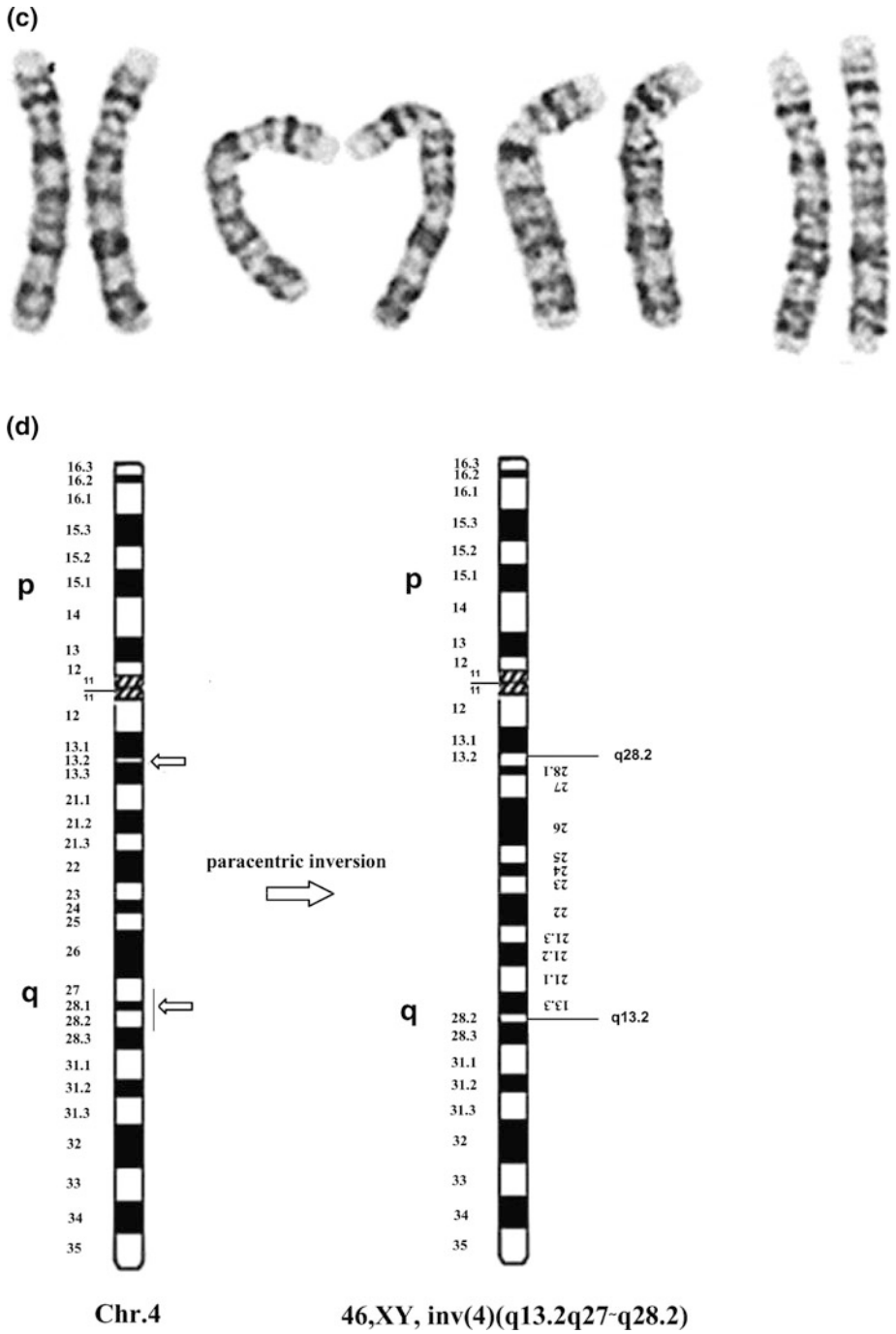

Fig. 4.22 (continued)

Case 23: Karyotype: 46,XY,inv(5)(p11p15.1)
Morphology:

The inverted segment comprises about 70% of the short arm and 15% of the total length of chromosome 5. The proximal breakpoint is located in the pericentromeric, heterochromatic region, the distal one in the GC-rich band p15.1. The AT-rich band p14 is now located more proximal and this leads to an abnormal banding pattern and therefore this inversion can even be diagnosed at a resolution of 400–550 bands per genome.

Cave:

According to the literature this small paracentric inversion only presents with a low genetic risk, but it has to be taken into account that the whole Cri-du-chat critical region is included and this has to be mentioned in the course of genetic counseling (Fig. 4.23).

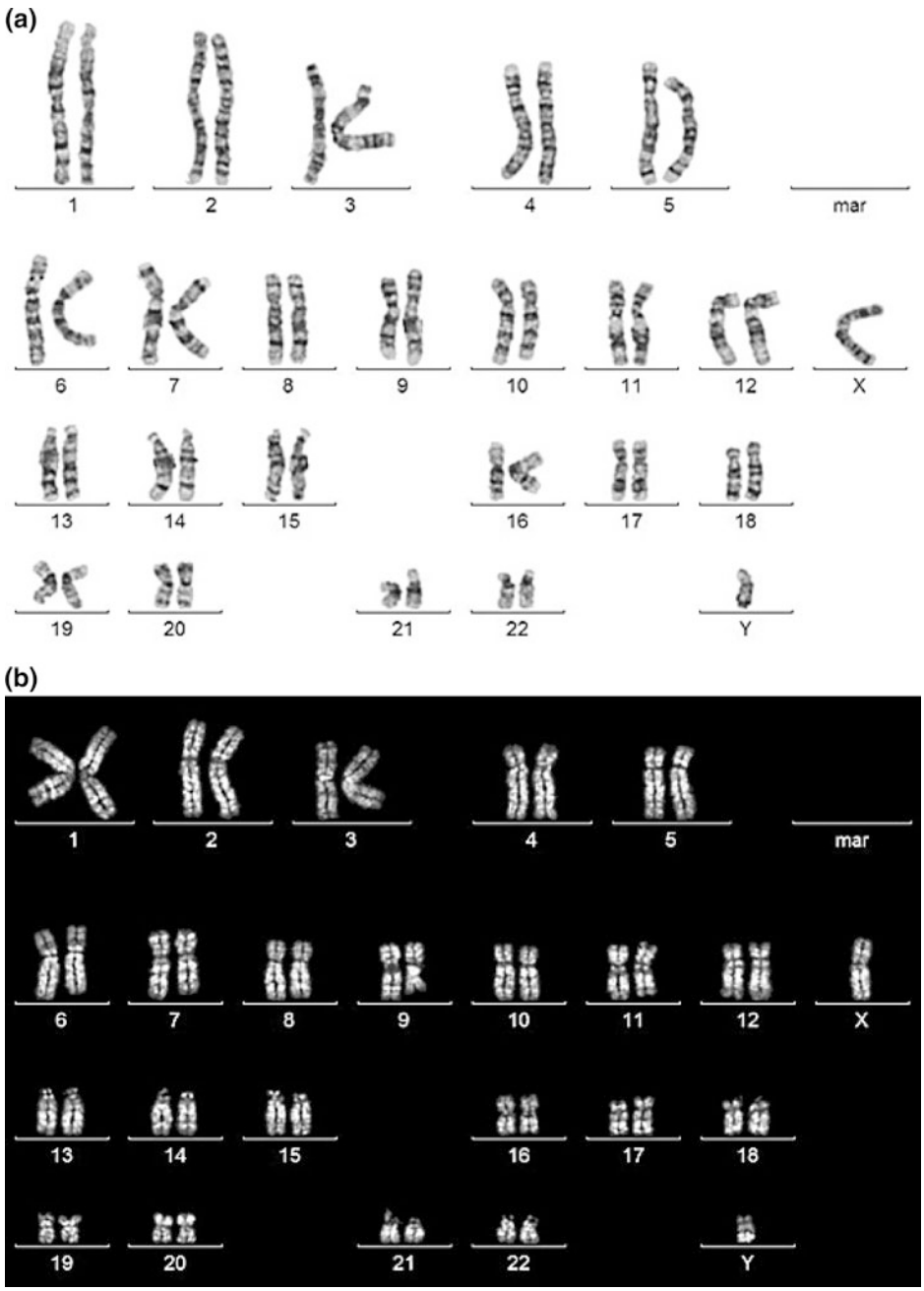

Fig. 4.23 Karyotype 46,XY,inv(5)(p11p15.1). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 5, **e** ideograms of chromosome 5, proximal breakpoint in the pericentromeric heterochromatin

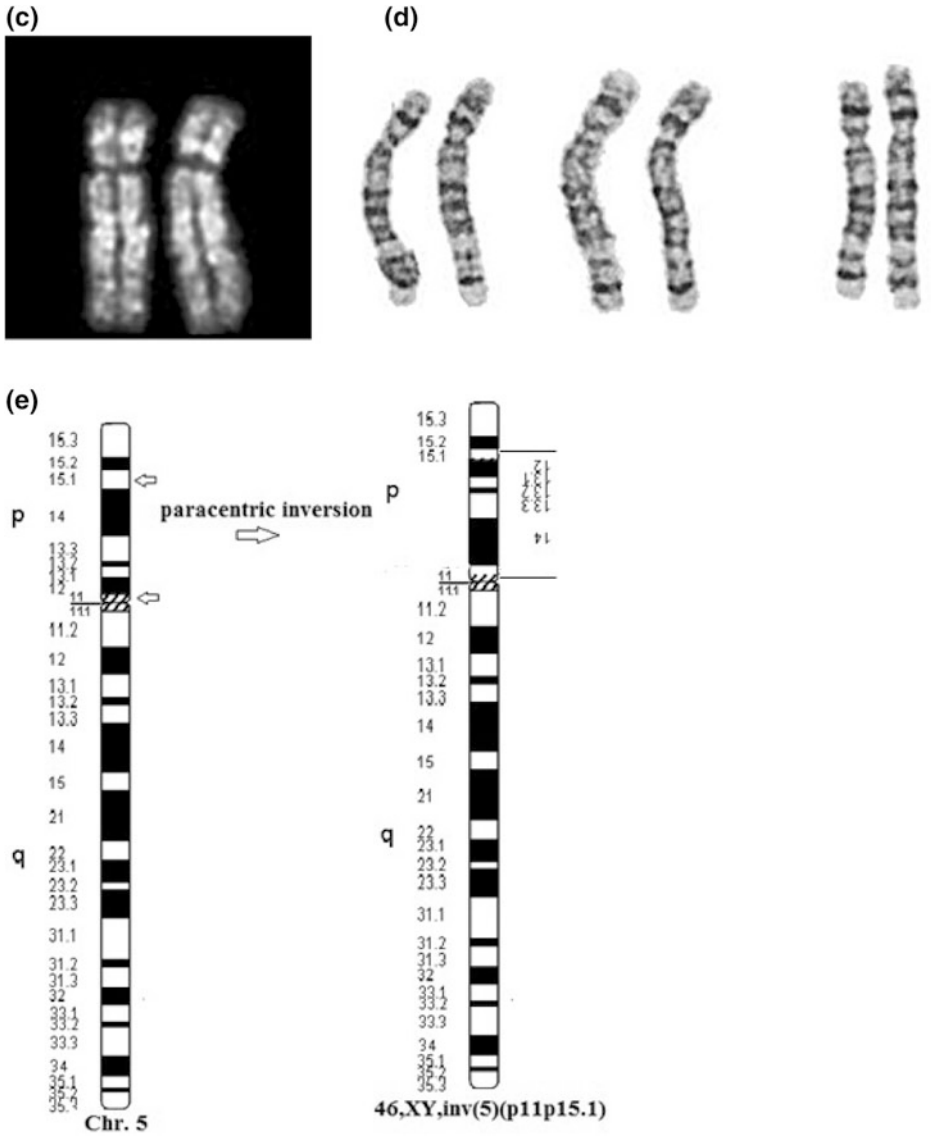

Fig. 4.23 (continued)

Case 24: Karyotype: 46,XX,inv(6)(q16.2q24.2)
Morphology:

The rearrangement occurred in an intermediate segment of the long arm of chromosome 6. The inverted region comprises about 25% of the total length of chromosome 6. This inversion is an excellent example to demonstrate the relevance of a high banding resolution to analyse an inversion in an almost homogenous banded segment. The exact diagnosis affords a resolution of 700–850 bands per genome.

Cave:

According to the literature on paracentric inversions, this rare type of rearrangement is estimated to have a low genetic risk. But specific data are not available (Fig. 4.24).

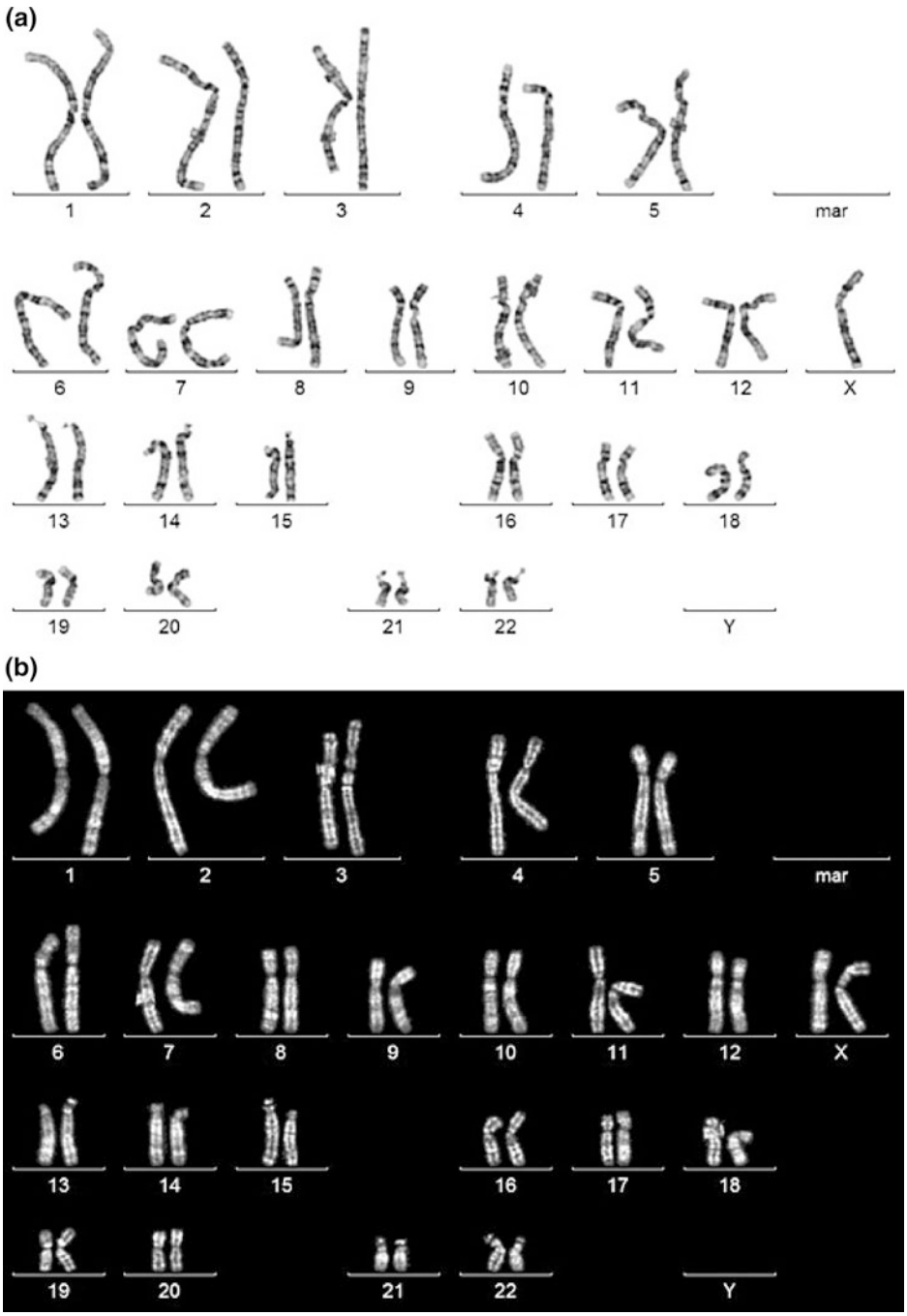

Fig. 4.24 Karyotype 46,XX,inv(6)(q16.2q24.2). **a** GTG-banding, 1 X-chromosome got lost during preparation, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 6, **e** ideograms of chromosome 6, Intermediate position in the long arm of the inverted segment

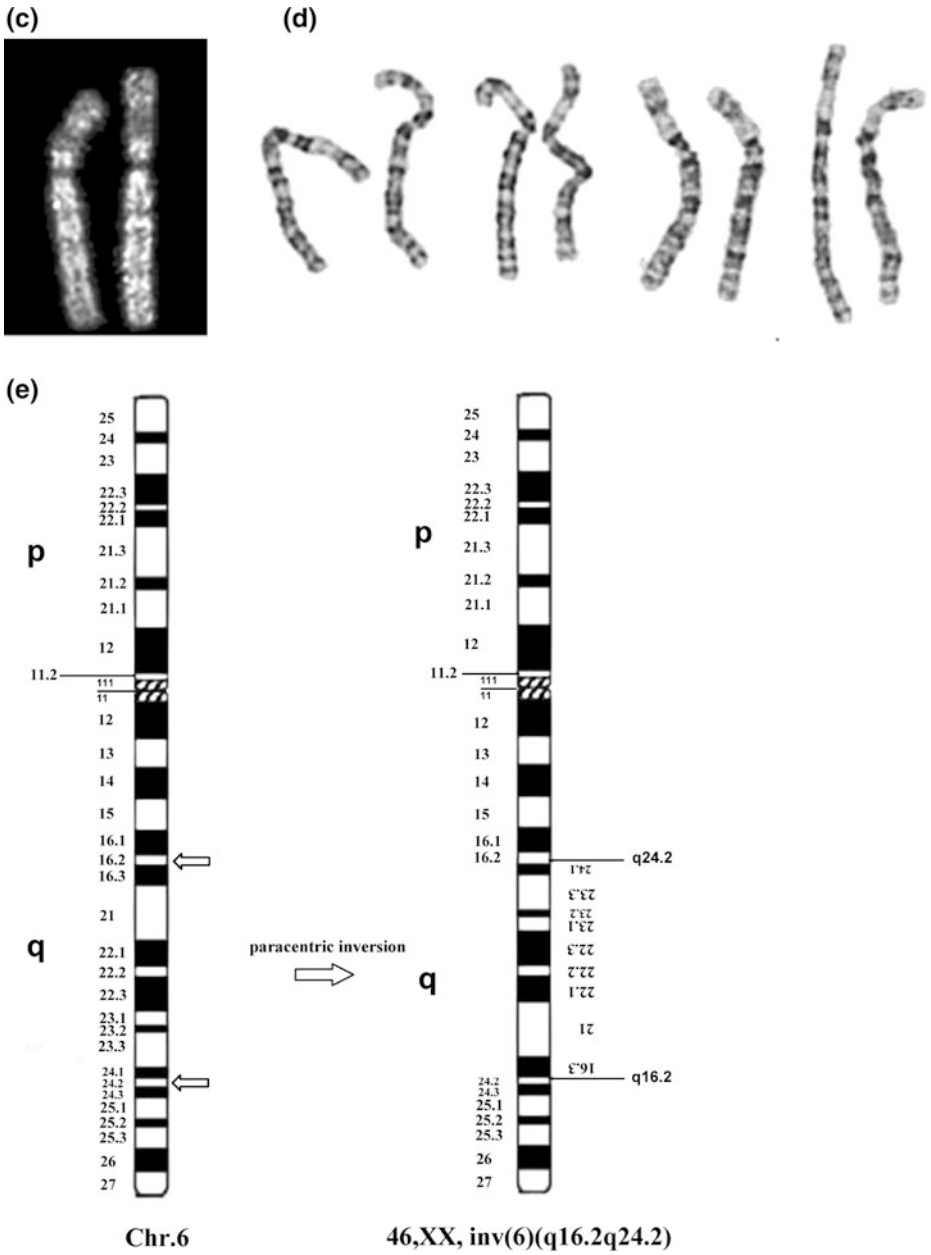

Fig. 4.24 (continued)

Case 25: Karyotype: 46,XY,inv(6)(q23.3q25.3)
Morphology:

Presented here is a small inversion in the distal part of the long arm of chromosome 6. The inverted region has a size of about 12% of the total length of the chromosome. For diagnosis there must be chosen a resolution of at least 550 bands per genome. Both breakpoints in 6q have been repeatedly described in pericentric inversions and in reciprocal translocations.

Cave:

Surveys from the literature on paracentric inversions of comparable size show a high genetic stability and therefore a low genetic risk for the carrier. This should be discussed with the carrier (Fig. 4.25).

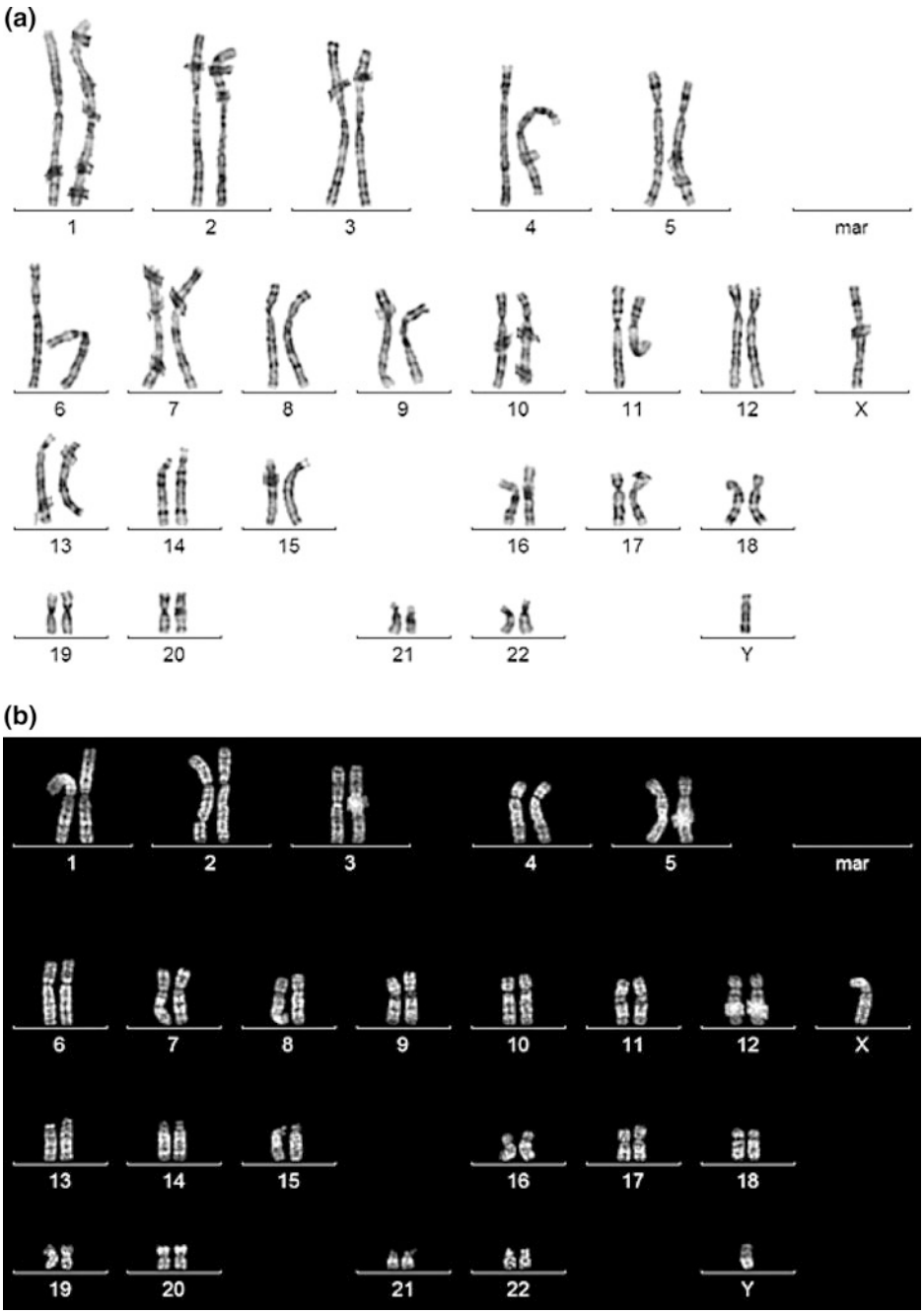

Fig. 4.25 Karyotype 46,XY,inv(6)(q23.3q25.3). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 6, **e** ideograms of chromosome 6, small, distal inversion in the long arm

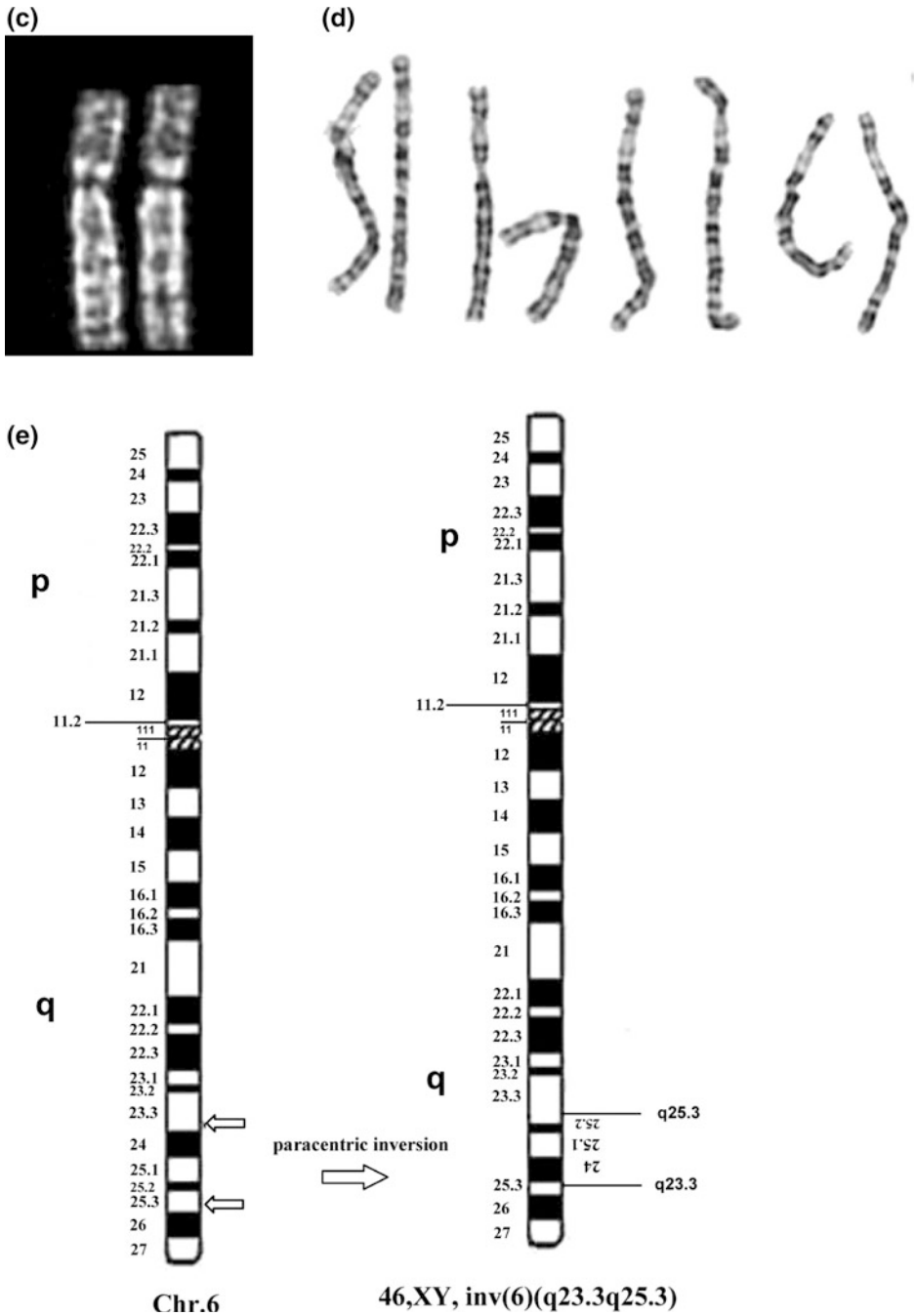

Fig. 4.25 (continued)

Case 26: Karyotype: 46,XX,inv(6)(q25.1q25.3)
Morphology:

This paracentric inversion in the distal part of the long arm is one of the smallest in the own investigation group, comprising only 4% of the total length of chromosome 6. It could be only analysed in metaphases with a resolution of more than 700 bands per genome. The survey of inversion chromosomes 6 from different mitoses makes this quite obvious.

Cave:

There is no sufficient information on paracentric inversions of chromosome 6 in this small size. Relying on general risk of chromosome rearrangements with euchromatic break points this is estimated to be in the order of 3–7% caused by an unequal crossing over in meiosis (Fig. 4.26).

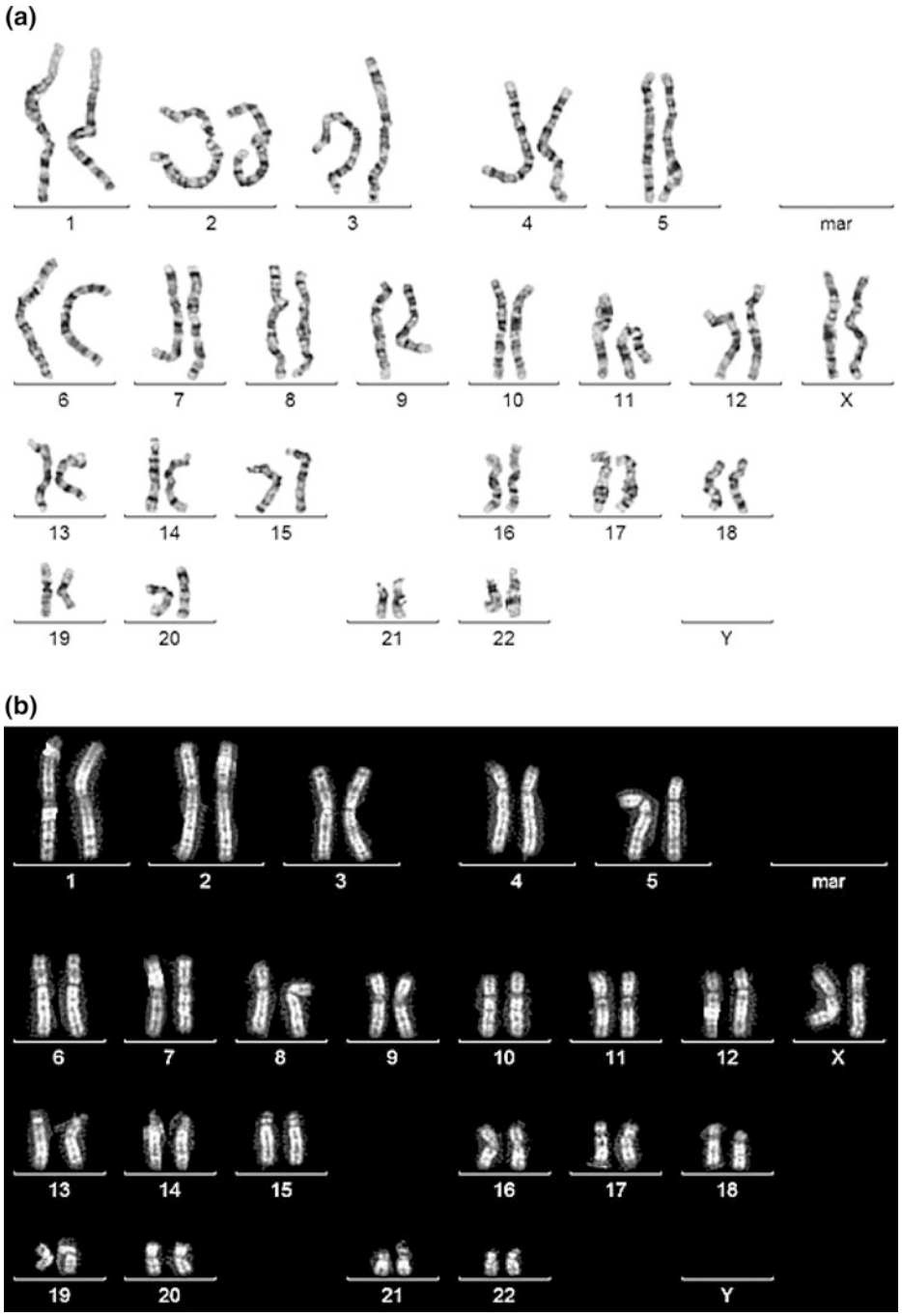

Fig. 4.26 Karyotype 46,XX,inv(6)(q25.1q25.3). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 6, **e** ideograms of chromosome 6, smallest inversion in the investigation group

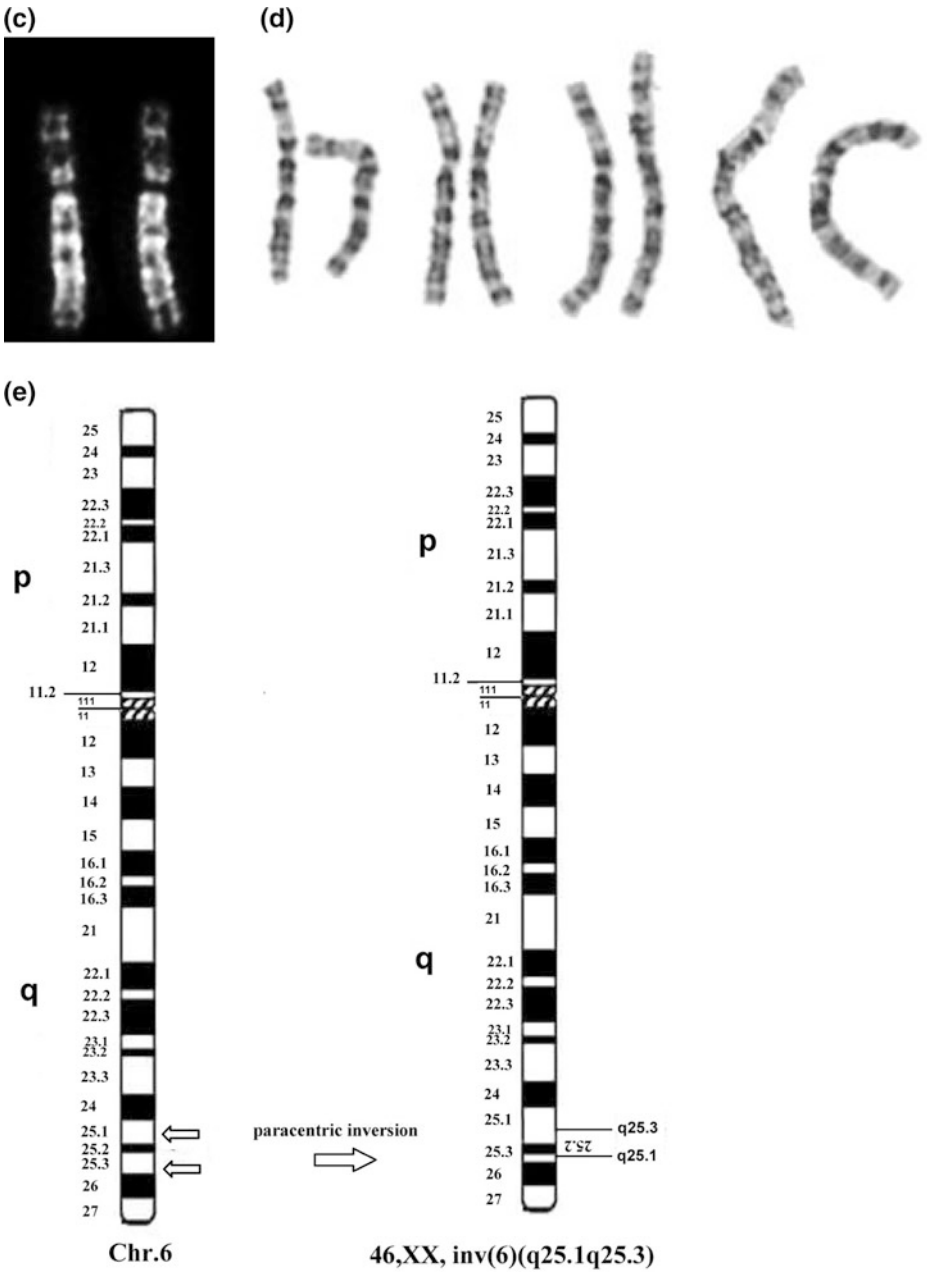

Fig. 4.26 (continued)

Case 27: Karyotype: 46,XX,inv(7)(p14.2p21.2)
Morphology:

The paracentric inversion presented comprises about 50% of the length of the short arm and 18% of the total length of the chromosome. The diagnosis of the rearrangement is performed in a first step by a changed position of the band p21.2 to a localisation more proximal. For the analysis of the second breakpoint p14.2 a resolution of 550–700 bands per genome is necessary.

Cave:

When delineating the genetic risk of the carrier possible epigenetic alterations have also to be taken into account. In this case, it is recommended to contact colleagues whose work focusses on this field (Fig. 4.27).

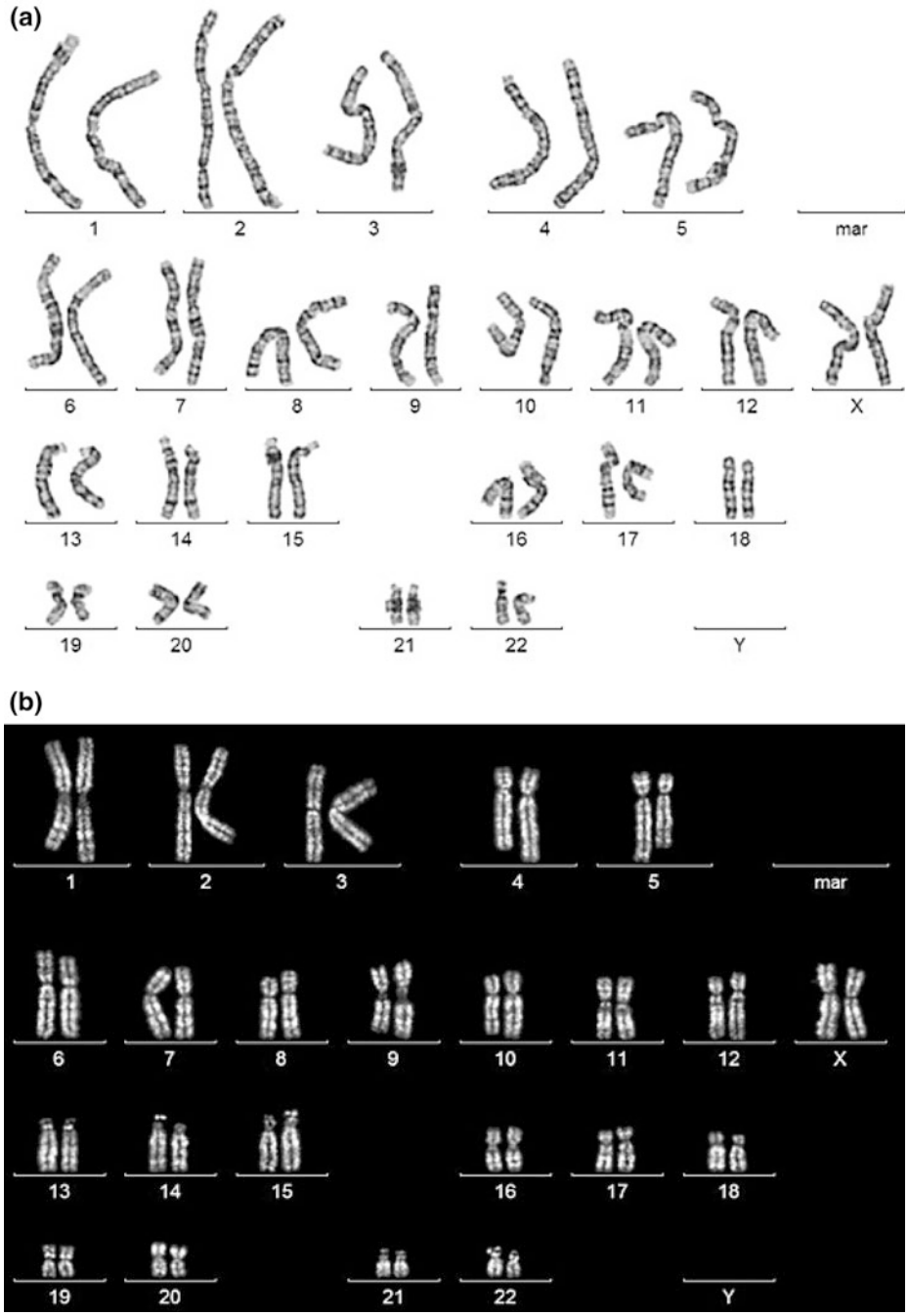

Fig. 4.27 Karyotype 46,XX,inv(7)(p14.2p21.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 7, **e** ideograms of chromosome 7, inverted segment of medium size

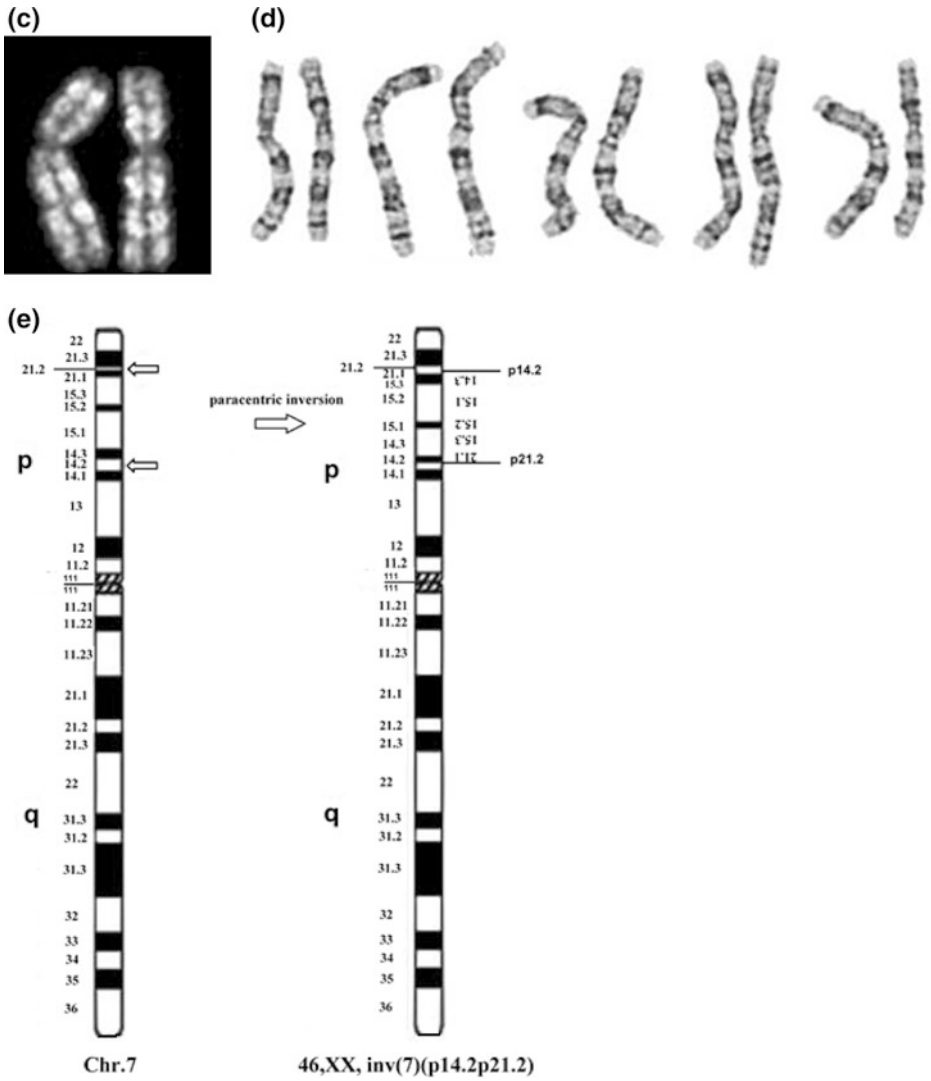

Fig. 4.27 (continued)

Case 28: Karyotype: 46,XY,inv(8)(q13q24.22)
Morphology:

The inverted region in the long arm comprises about 40% of the total length of chromosome 8. A characteristic feature of this inversion is the changed position of 8q23 to a more proximal localisation, which enables a quick and safe diagnosis. The distal breakpoint seems to be a hot-spot for aberration induction, as different types of rearrangements like deletions, rings, and translocations have been described with this breakpoint.

Cave:

In the region 8q24.11q24.13 the mutation, mainly a deletion of the Langer-Giedion-syndrome is localised. Therefore, when analysing an inversion including this region it is of special relevance to investigate if the position of a breakpoint is within or outside the critical region. Thus, when analysing a comparable inversion the resolution of the chromosome bands should be 550–700 bands per genome. If the breakpoint can be located in the critical region an additional microarray analysis has to be done. Genetic counseling has to be recommended and prenatal investigation should always be completed by microarray (Fig. 4.28).

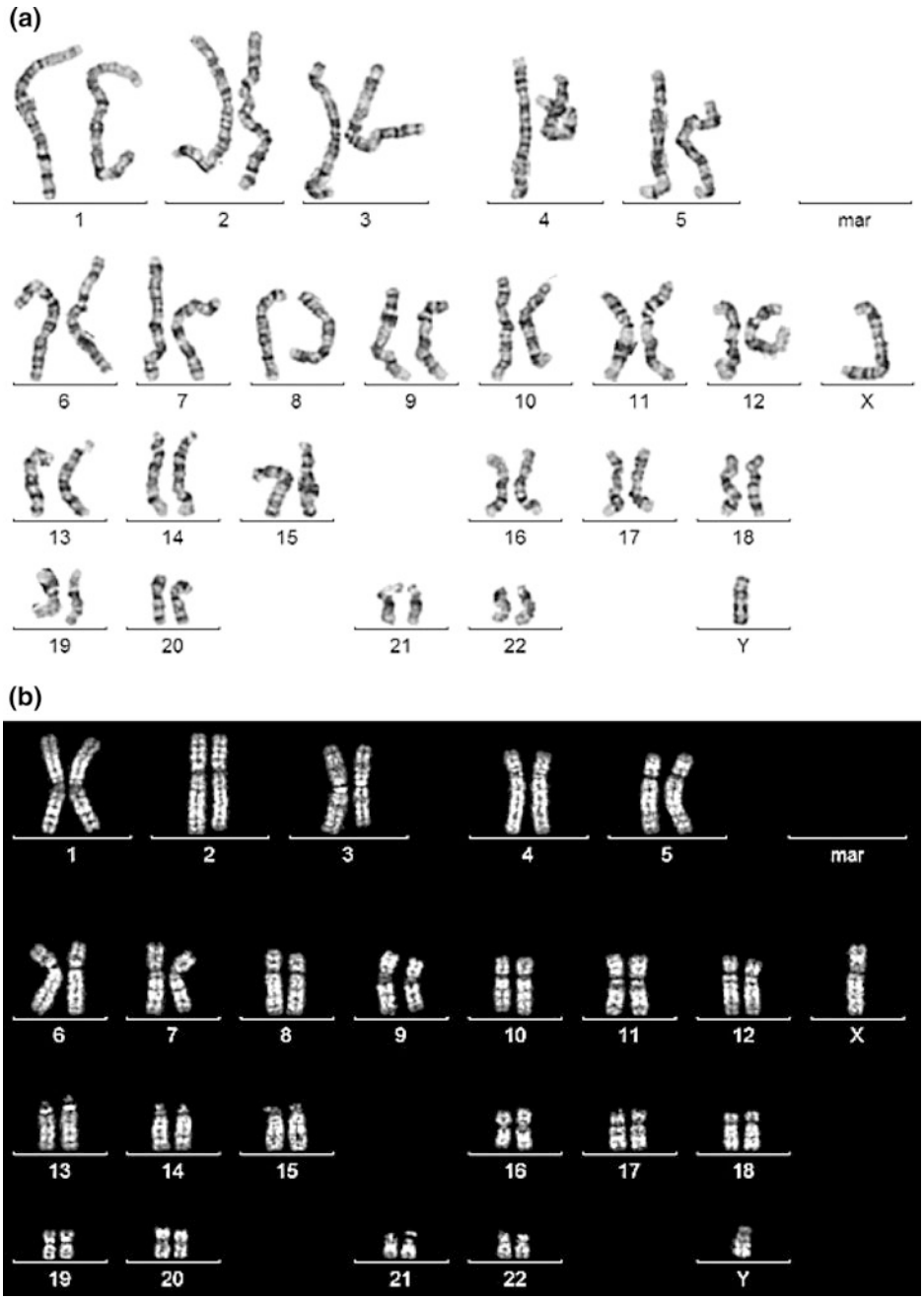

Fig. 4.28 Karyotype 46,XY,inv(8)(q13q24.22). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 8, **e** ideograms of chromosome 8, medium to large size of the inverted segment

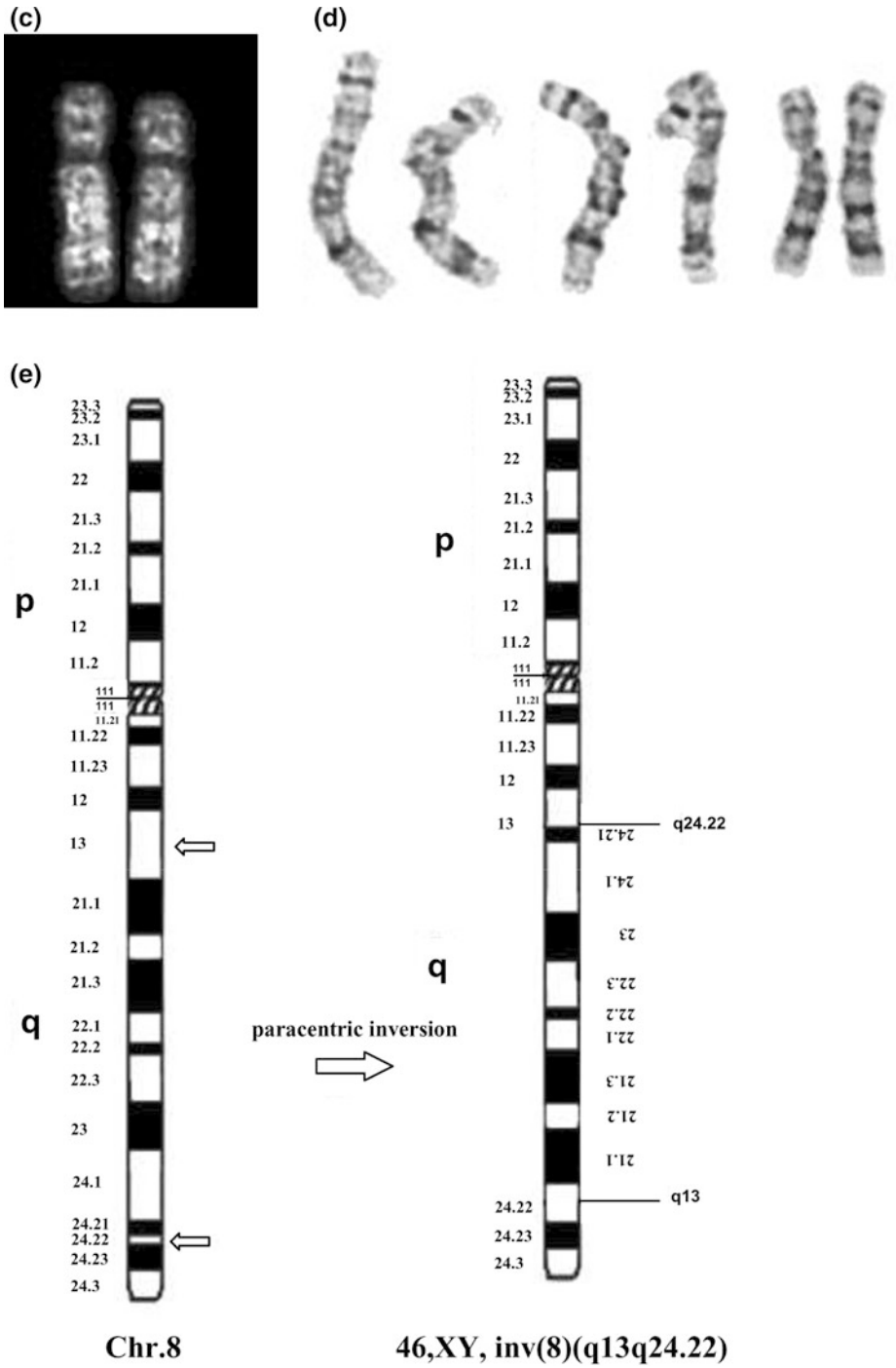

Fig. 4.28 (continued)

Case 29: Karyotype: 46,XY,inv(9)(q32q34.3)
Morphology:

This distal localised paracentric inversion 9 comprises about 15% of the total length of the chromosome. Caused by the dislocation of the AT-rich band q33, this inversion can be easily recognised even by a resolution of less than 550 bands per genome. But the exact localisation of the breakpoints requires a resolution of 550 bands.

Cave:

The distal breakpoint q34.3 is an aberration hot-spot. One of the three most frequent microdeletion syndromes is localised in this region. Furthermore the band q34 is a frequent breakpoint in rearrangements occurring in different tumor diseases (Fig. 4.29).

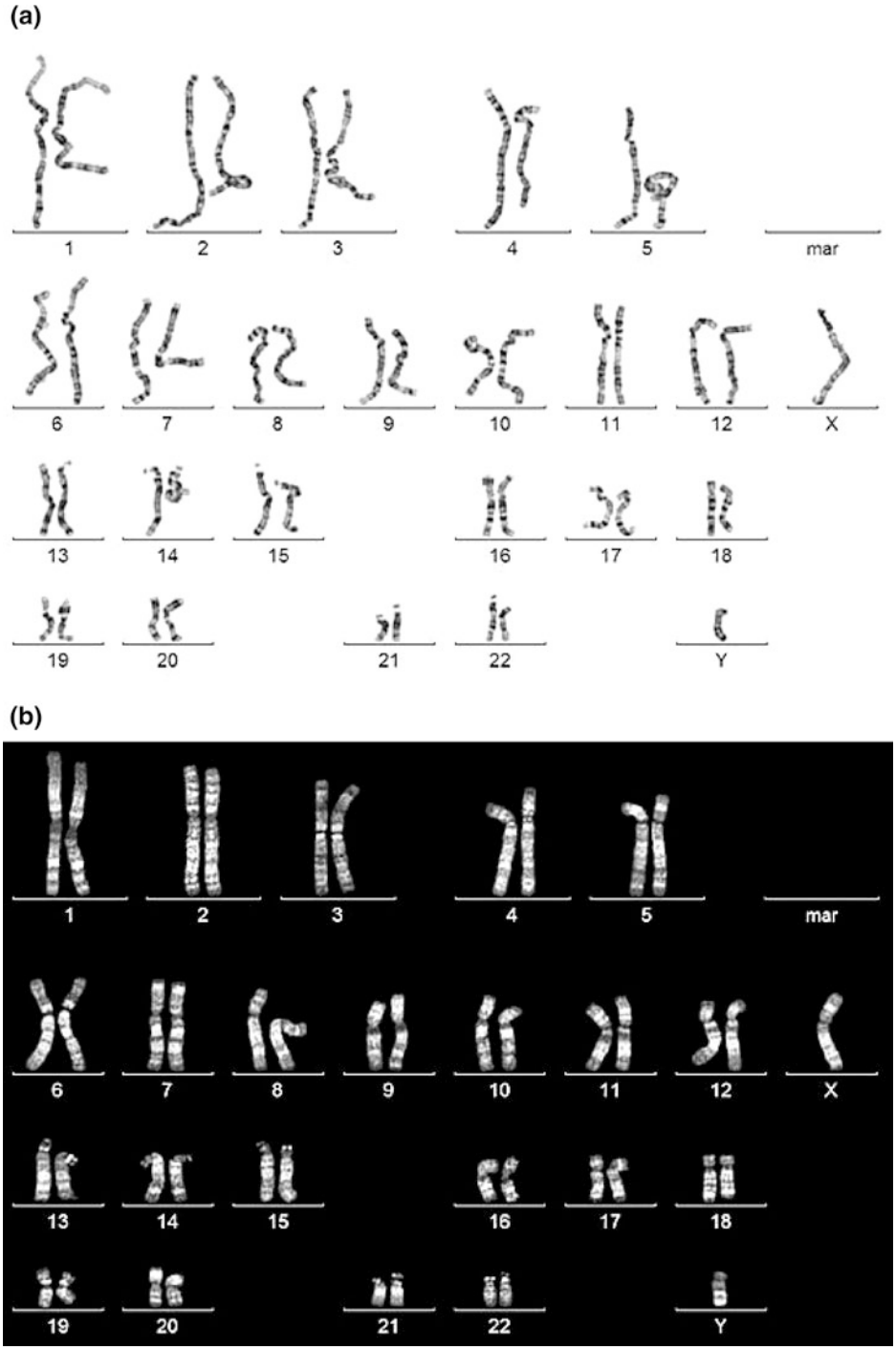

Fig. 4.29 Karyotype 46,XY,inv(9)(q32q34.3). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 9, **e** ideograms of chromosome 9, small distal inversion segment

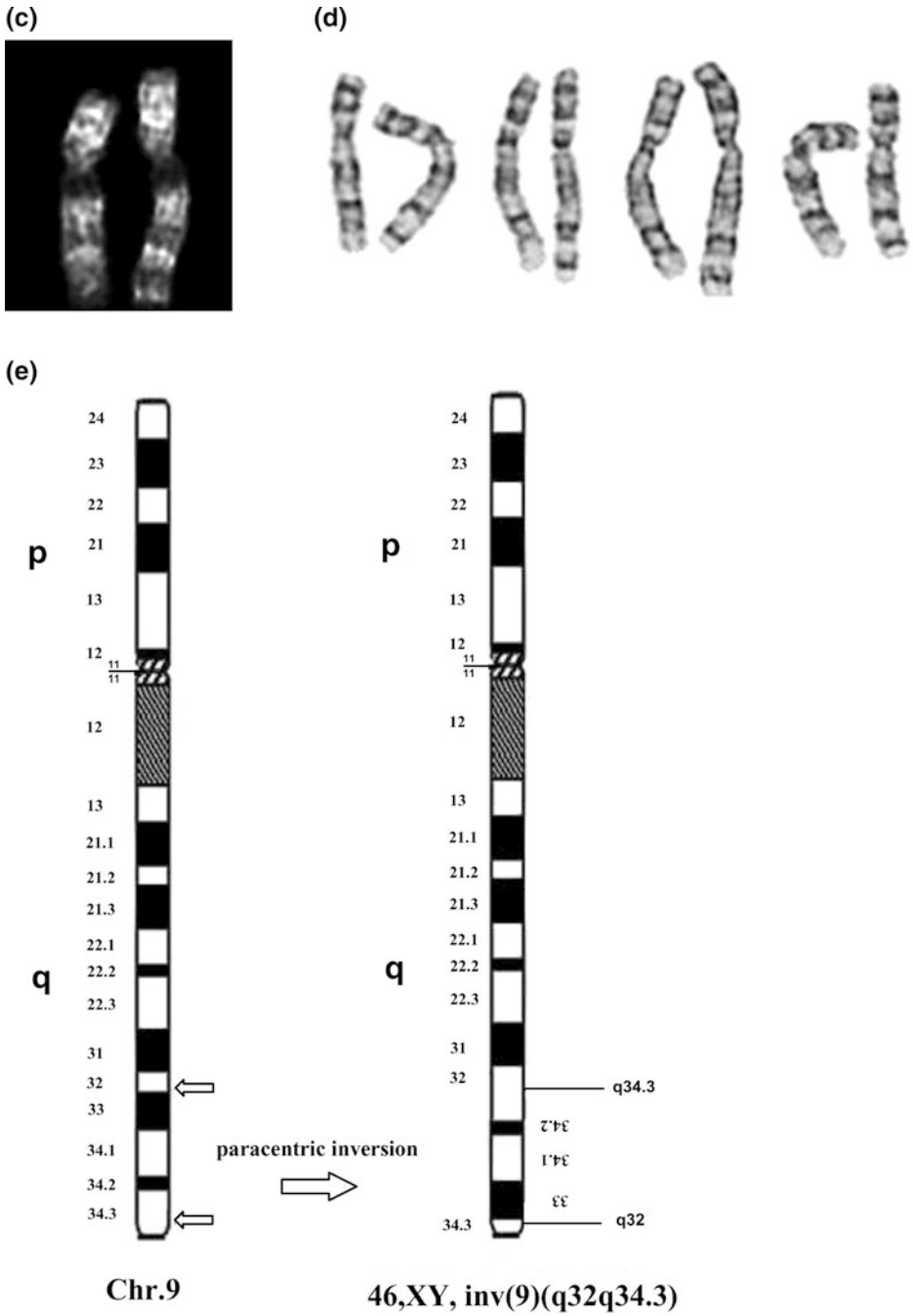

Fig. 4.29 (continued)

Case 30: Karyotype: 46,XX,inv(11)(q21q23.3)
Morphology:

The inverted region in the long arm comprises about 15% of the total chromosome length. The paracentric inversion 11 with the breakpoints of our case has been documented worldwide in different ethnic populations. Besides, a Founder-effect has been ascertained.

Cave:

In all family studies this inversion was stated to be stable and to be always inherited as a balanced rearrangement. Therefore, relying on our present knowledge, this inversion does not present with an increased genetic risk. Investigations of relatives of a carrier or prenatal analyses are not indicated (Fig. 4.30).

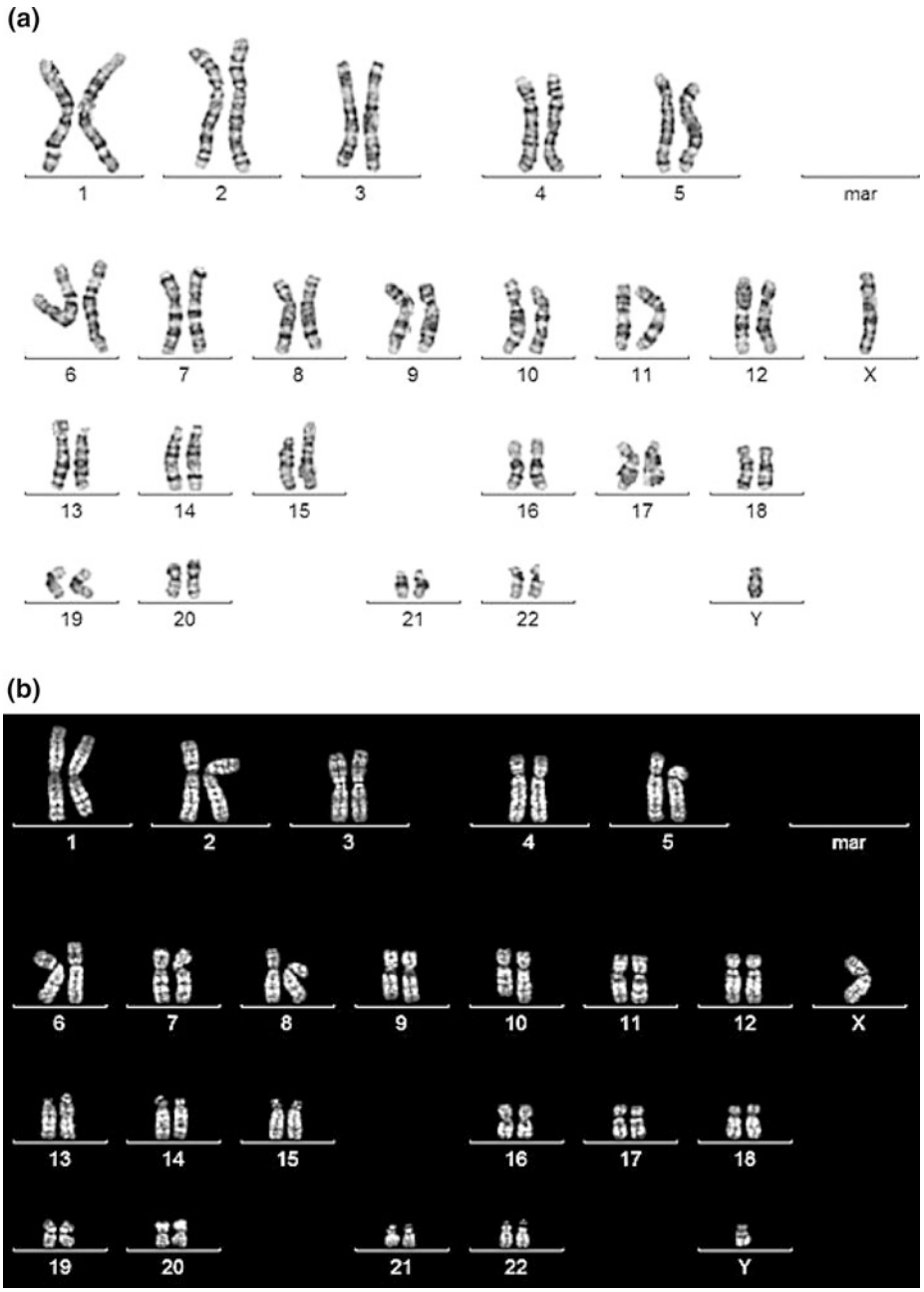

Fig. 4.30 Karyotype 46,XX,inv(11)(q21q23.3). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 11, **e** ideograms of chromosome 11, characteristic frequent breakpoints

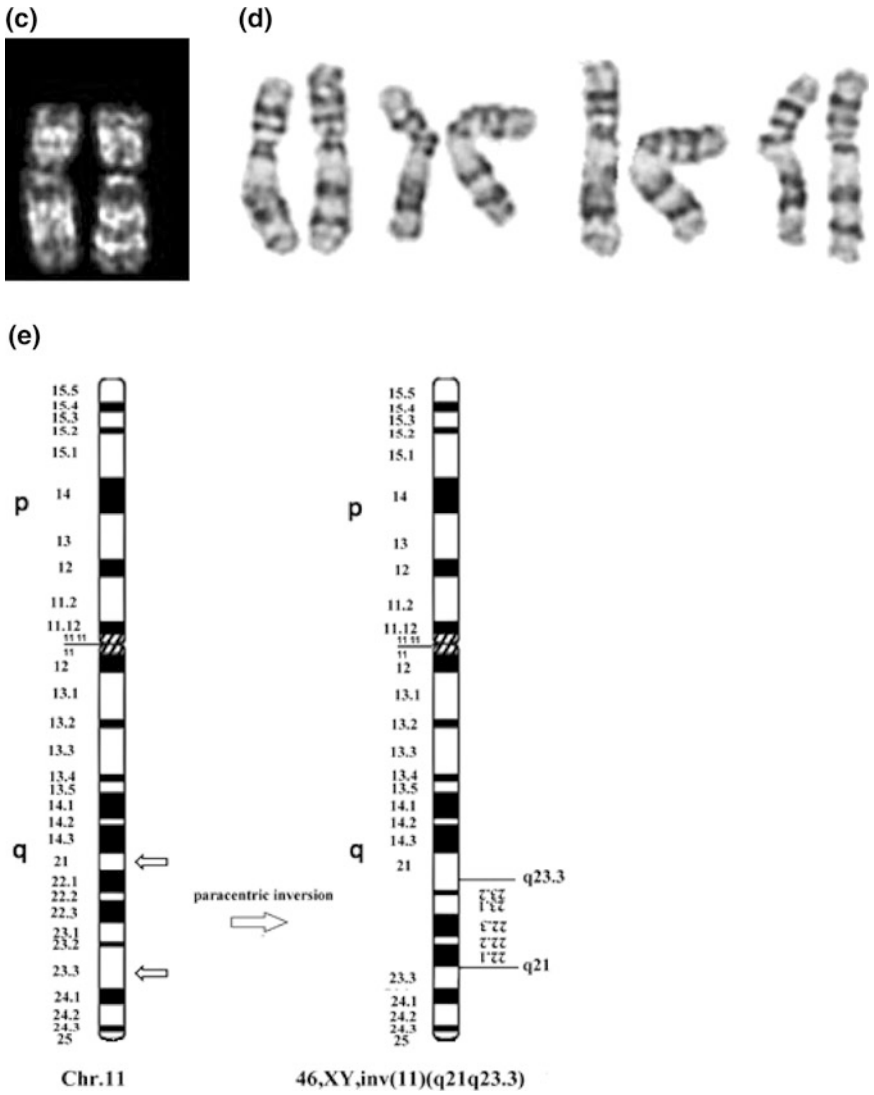

Fig. 4.30 (continued)

Case 31: Karyotype: 46,XX,inv(12)(q21.1q24.1)
Morphology:

Presented here is a medium-sized, intermediate inversion in the long arm of chromosome 12, which comprises about 25% of the total length of the chromosome. The dislocation of band q23 leads to a striking altered banding pattern, already detectable at a resolution of 400–550 bands per genome, but the exact localisation of the breakpoints affords a higher resolution.

Cave:

According to the literature the genetic risk for the carrier is low. This has to be taken into account when counseling the carrier and his family (Fig. 4.31).

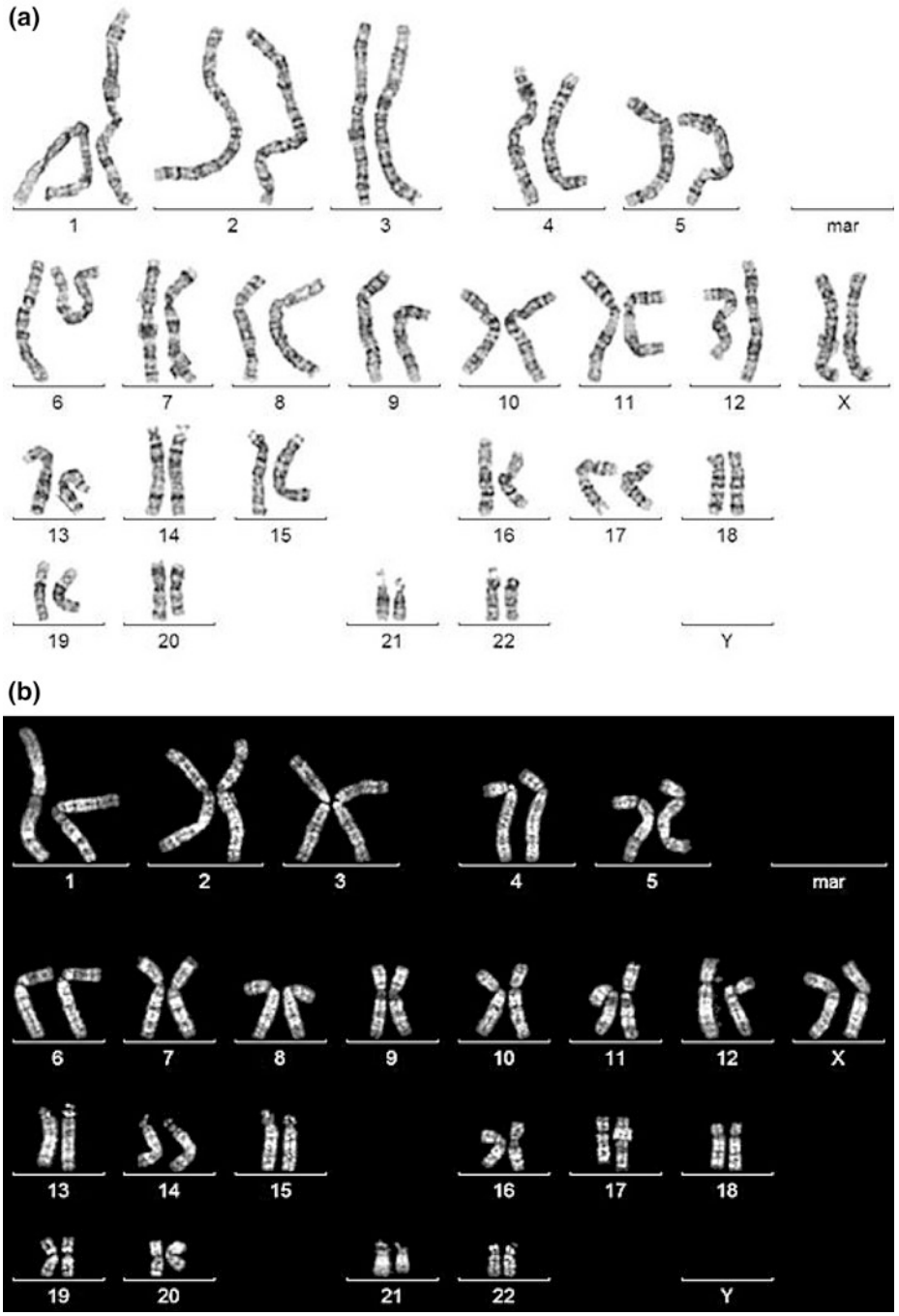

Fig. 4.31 Karyotype 46,XX,inv(12)(q21.1q24.1). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 12, **e** ideograms of chromosome 12, intermediate breakpoints in the long arm

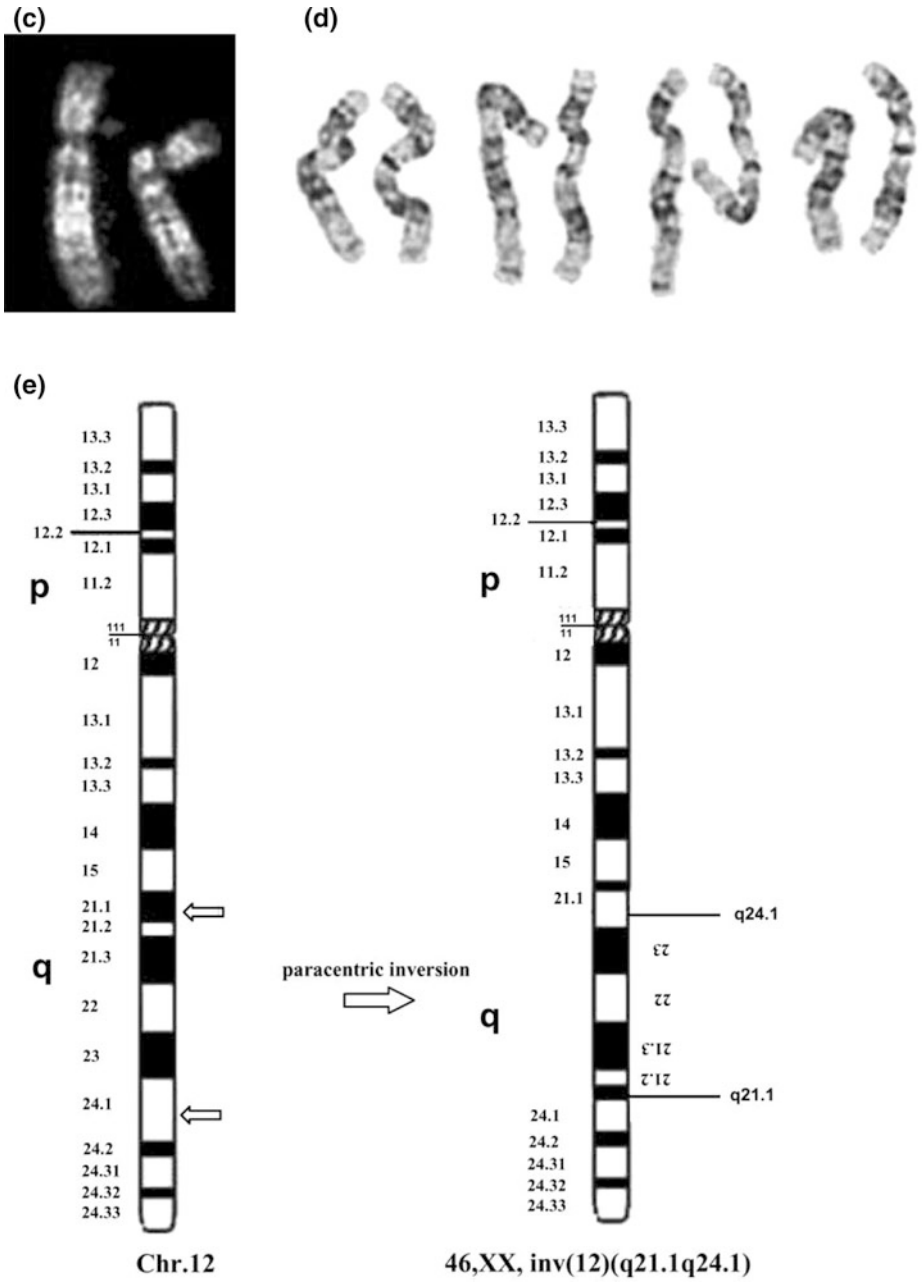

Fig. 4.31 (continued)

Case 32: Karyotype: 46,XX,inv(13)(q12.1q22)

The inversion comprises about 50% of the euchromatic long arm, and 40% of the total length of chromosome 13. By the altered banding pattern in the proximal and intermediate region it is easy to recognize.

Cave:

According to the literature the genetic risk of the carrier is low. Therefore the possibilities of prenatal diagnosis should be discussed but there is no reason for a recommendation (Fig. 4.32).

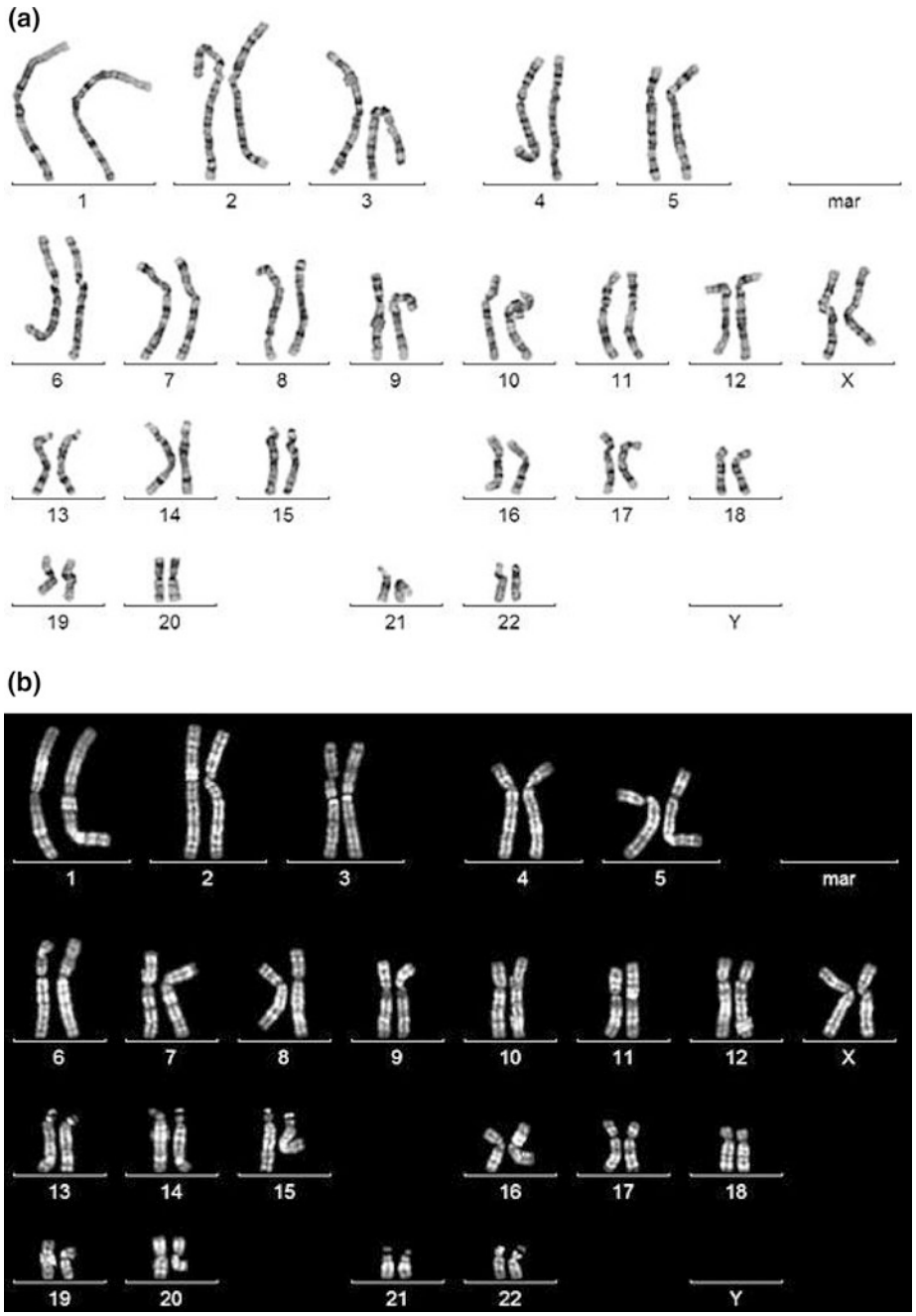

Fig. 4.32 Karyotype 46,XX,inv(13)(q12.1q22). **a** GTG-, **b** QFQ-banding, 700 and 550 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 13, **e** ideograms of chromosome 13, large inverted segment

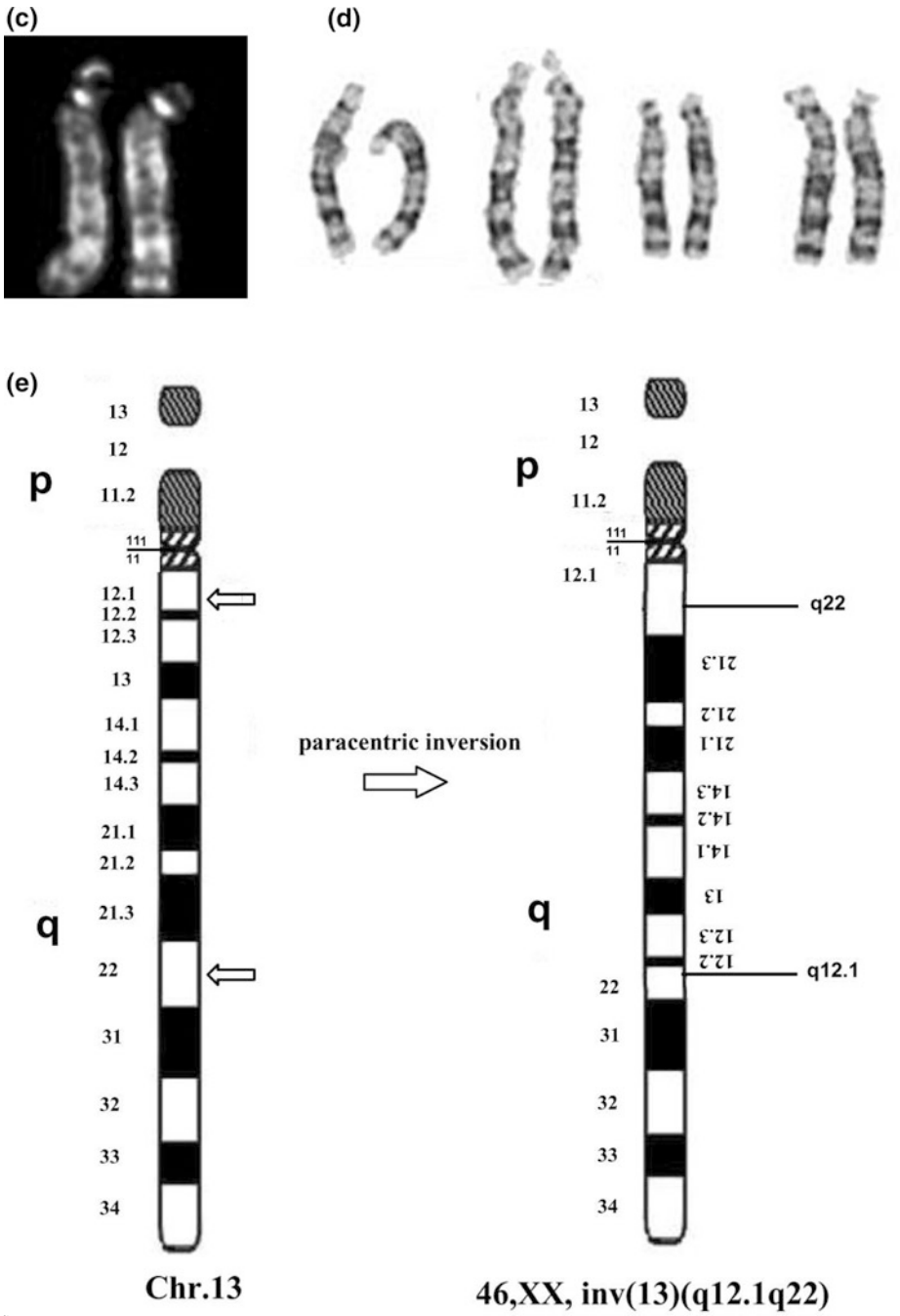

Fig. 4.32 (continued)

Case 33: Karyotype: 46,XY,inv(13)(q13q32)
Morphology:

This paracentric intermediate inversion 13 comprises about 60% of the length of the euchromatic long arm and 50% of the total length of the chromosome. The banding pattern is characteristically changed by shifting of the AT-rich bands q21 and q31.

Cave:

The inverted region in this case is larger than in the previous one, thus it is attributed to cases with increased genetic risk. Genetic counseling should give the advice for the investigation of relatives and for prenatal diagnosis (Fig. 4.33).

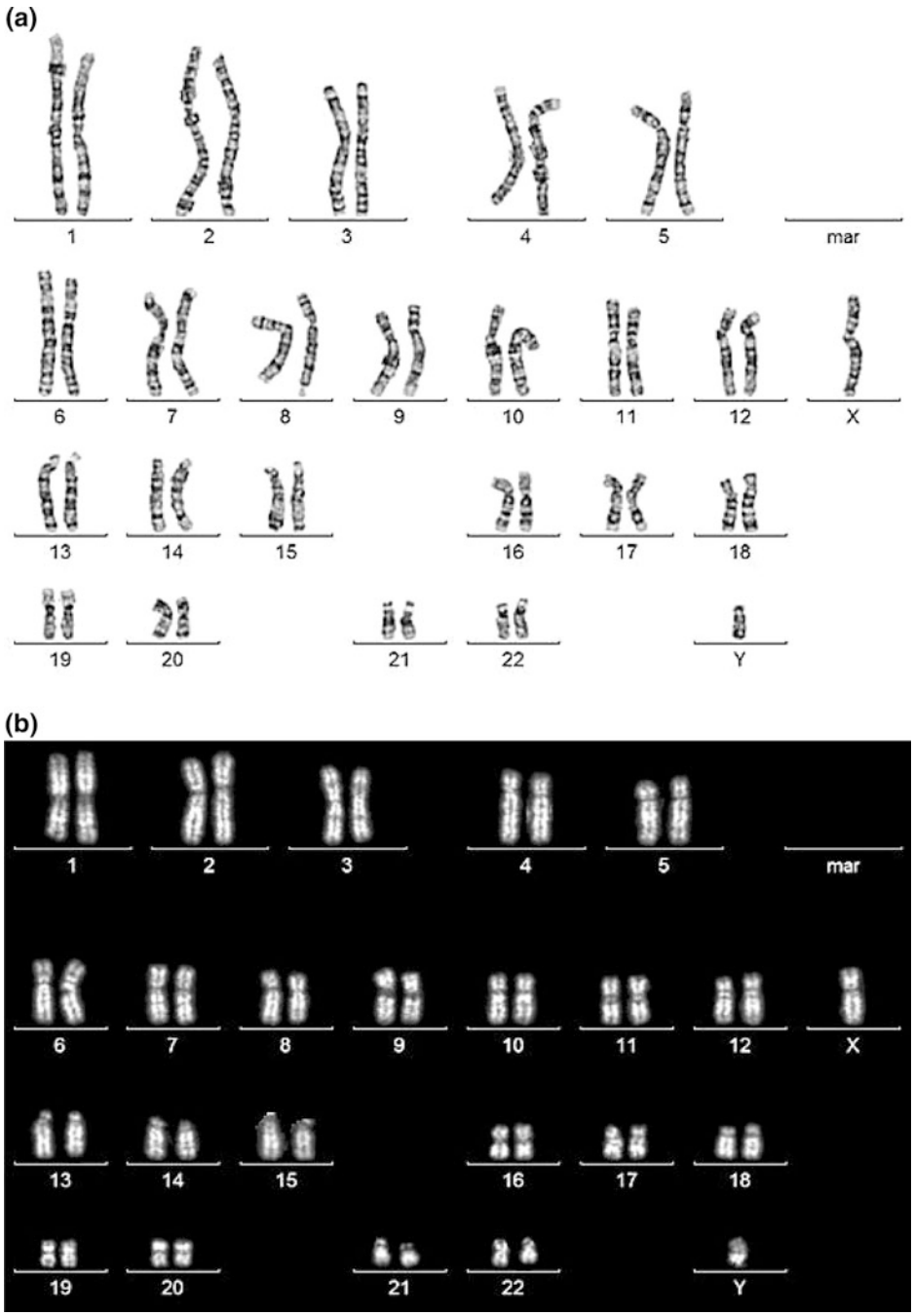

Fig. 4.33 Karyotype 46,XY,inv(13)(q13q32). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 13, **e** ideograms of chromosome 13, large inverted segment

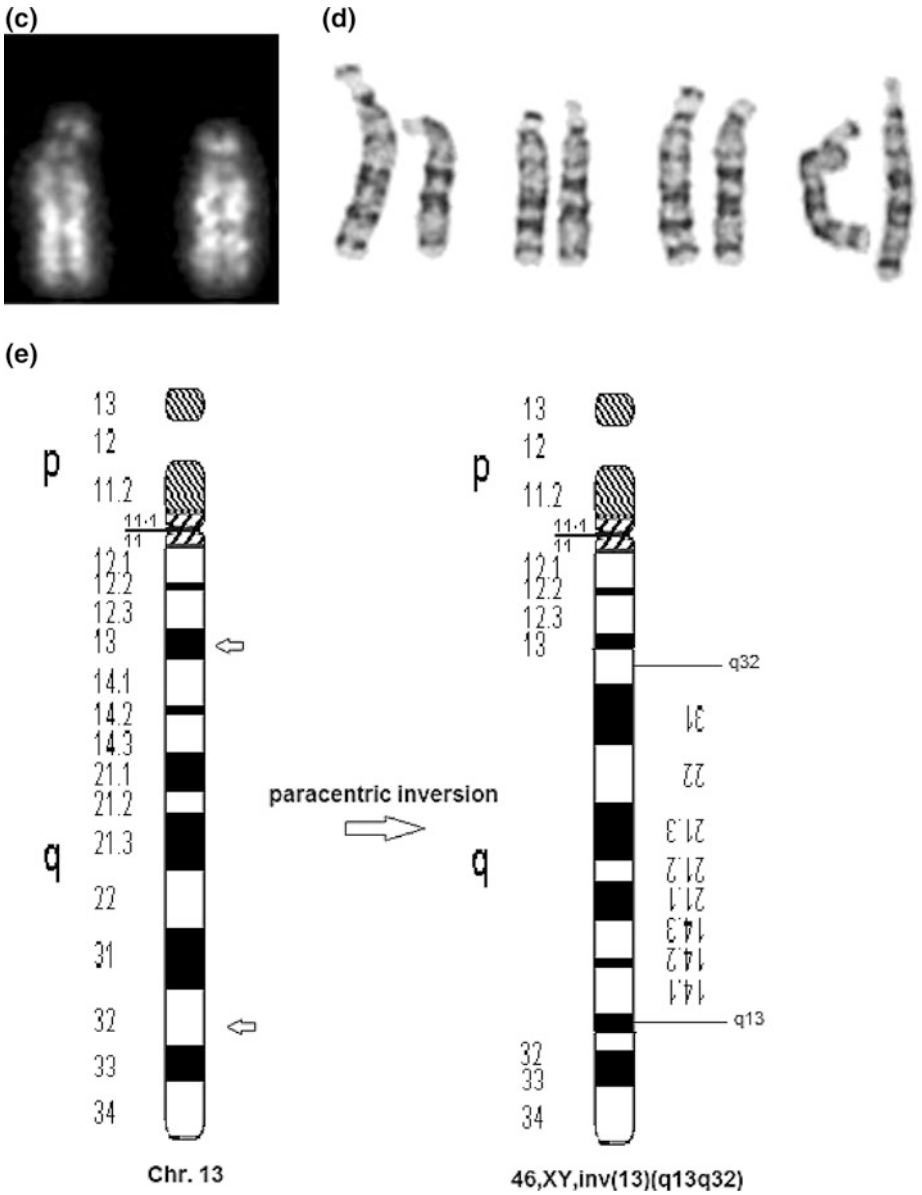

Fig. 4.33 (continued)

Case 34: Karyotype: 46,XX,inv(13)(q21.2q31)
Morphology:

This paracentric inversion 13 presents with a rearrangement in the intermediate region of the long arm. The inverted segment comprises about 25% of the euchromatic long arm and about 20% of the total length. The AT-rich bands q21 and q31 have changed their position and thus lead to an altered banding pattern. For the analysis of the inversion a resolution of 550–700 bands per genome is necessary, otherwise the relevant differentiation of q21 into the subbands q21.1, q21.2, q21.3 is not possible.

Cave:

The genetic risk and the consequences for the carrier are low (Fig. 4.34).

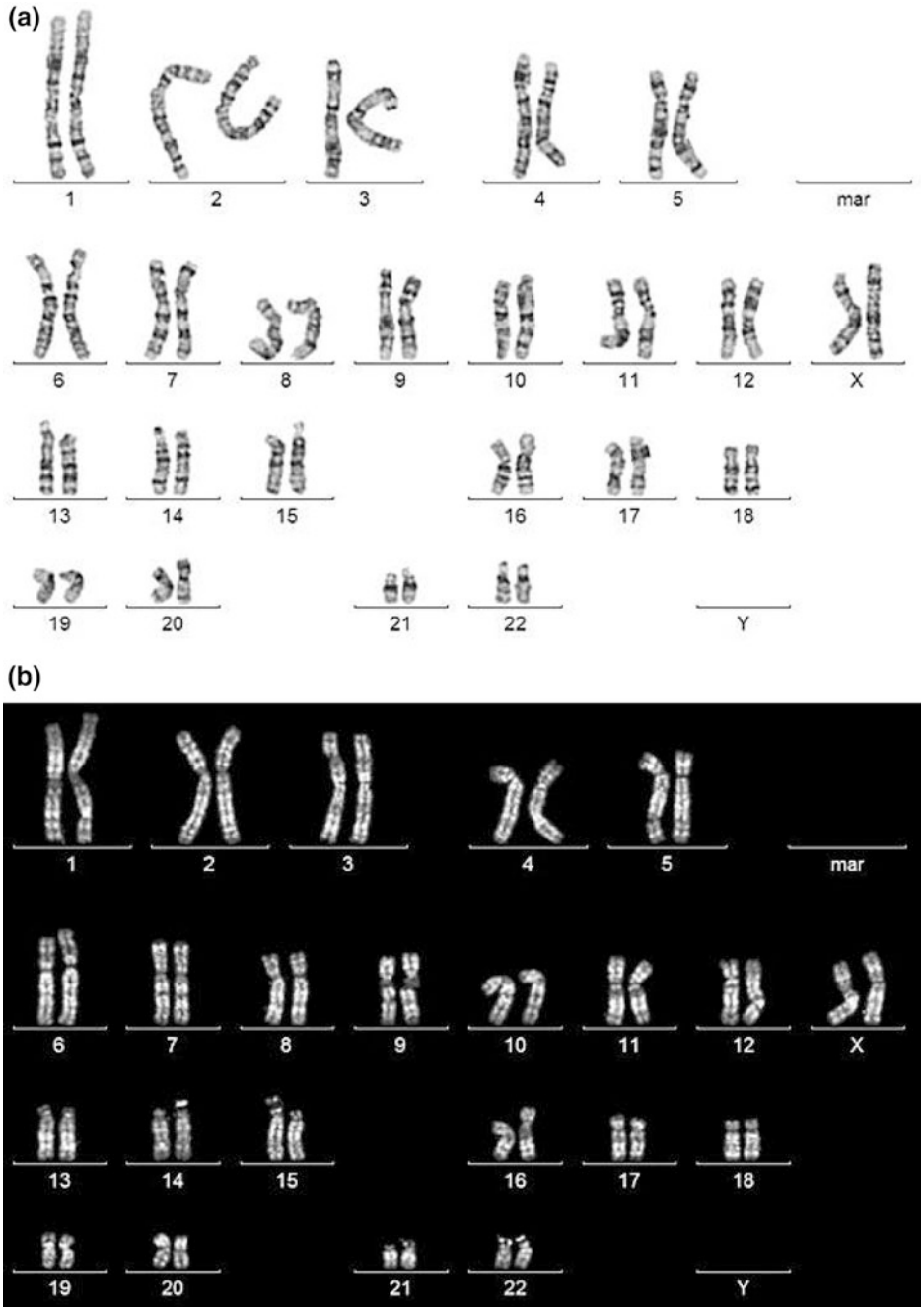

Fig. 4.34 Karyotype 46,XX,inv(13)(q21.2q31). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 13, **e** ideograms of chromosome 13, intermediate, medium-sized inverted segment

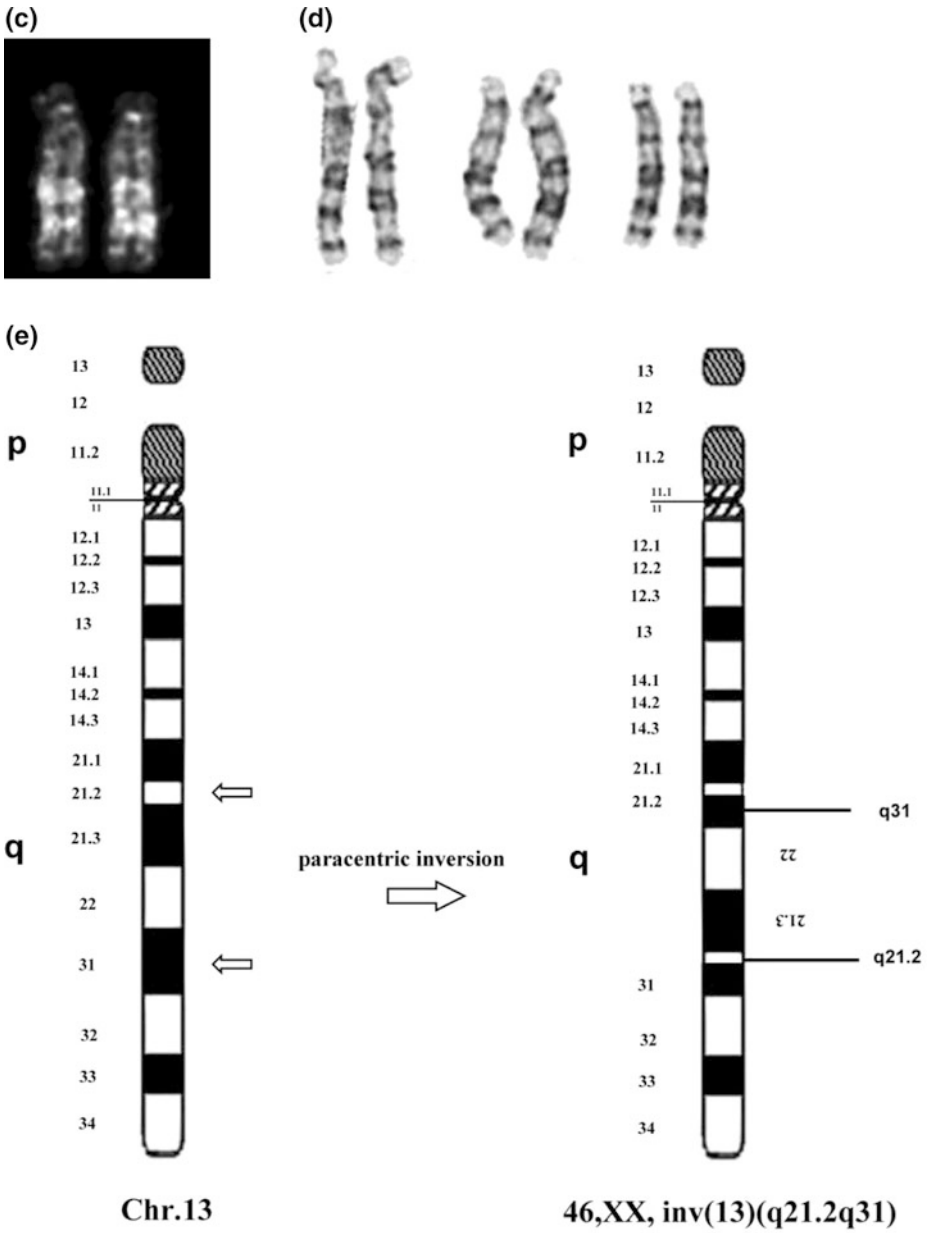

Fig. 4.34 (continued)

Case 35: Karyotype: 46,XX,inv(14)(q23.3q32.2),inv(3)(p11.2q12)(X2)
The proband shows three inversions (two in heterochromatic and one in euchromatic regions).

Morphology:

1. + 2. inv(3)(p11.2q12)(x2)
   This type of rearrangement is present in both chromosomes 3. Thus the carrier is homozygous for the inversion. The presentation of the centromere adjacent heterochromatic block is usually performed by QFQ-banding, leading to a brilliant fluorescence of the region (fluorescence intensity 5 according to ISCN). The inversion frequency in this genetic not relevant segment in the European population is about 2%.
3. inv(14)(q23.3q32.2)
   The rearrangement is localised in the intermediate to distal region of the long arm. It comprises about 40% of the euchromatic long arm and 50% of the total length of the chromosome. The banding pattern has changed by the dislocation of the subbands of the AT-rich bands q21 and q31.

Cave:

The analysis of a homozygosity of the inverted bands on chromosome 3 may be evidence that the carrier is descendant of parents which are related. This should be discussed in the course of genetic counseling. In the present case only the low genetic risk of the paracentric inversion 14 has to be discussed in the course of genetic counseling (Fig. 4.35).

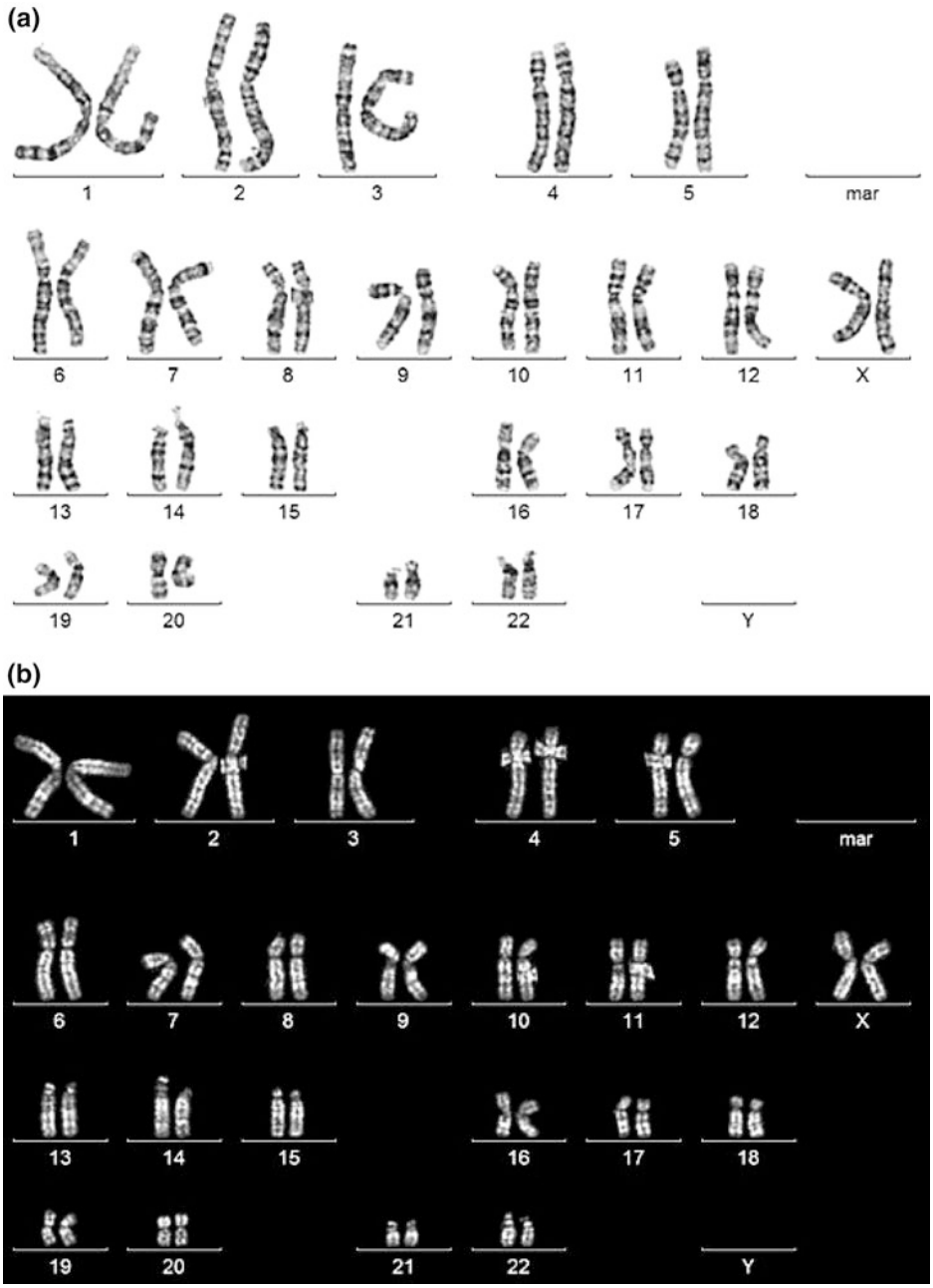

Fig. 4.35 Karyotype 46,XX,inv(14)(q23.3q32.2),inv(3)(p11.2q12)(x2). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c**, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, **c** both chromosomes 3 show the pericentric inversion of the heterochromatin block; **d**, **e** chromosome 14: *left* normal, *right* inverted chromosome, **f** ideograms of chromosomes 3 and 14, inv(3) restricted to pericentromeric heterochromatin in both homologues, inv(14) medium sized in the distal region

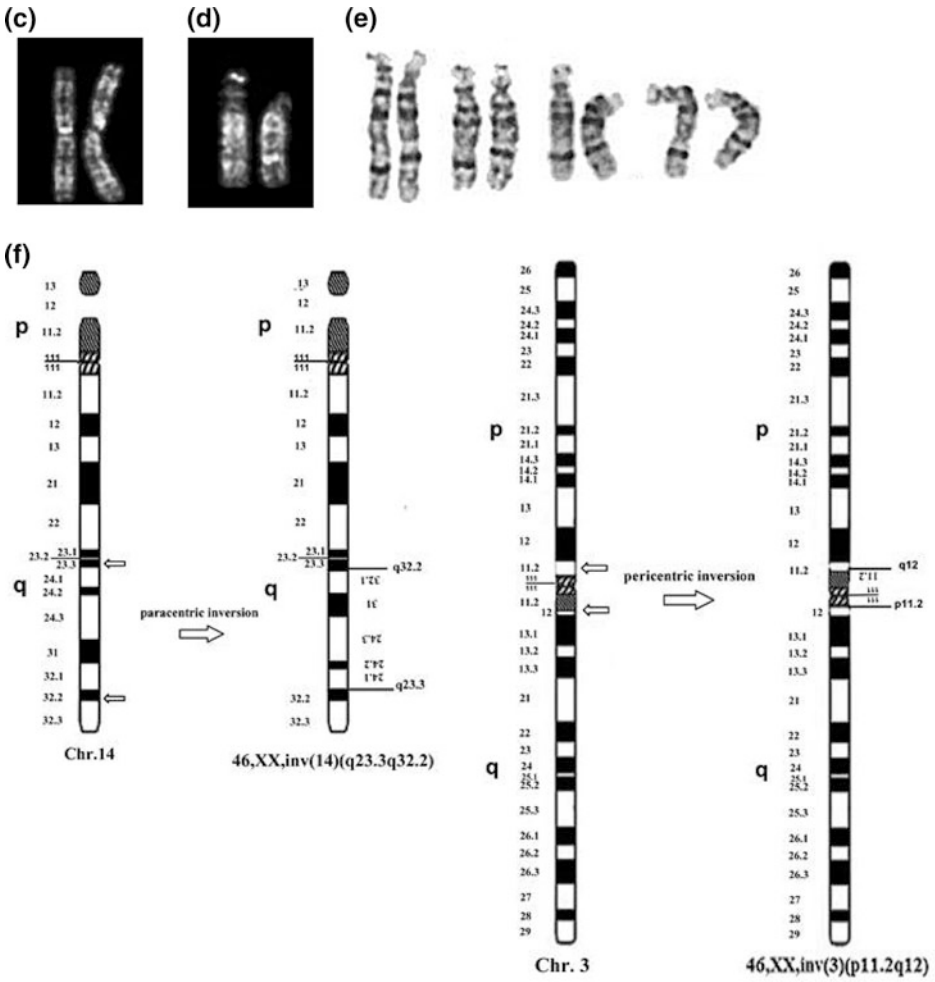

Fig. 4.35 (continued)

Case 36: Karyotype: 46,XX,inv(15)(q24q26.3)
Morphology:

This paracentric inversion is localised in the distal region of the long arm. The inversion comprises about 30% of the euchromatic long arm and 25% of the total length of the chromosome. Both breakpoints are localised in GC-rich regions and q26.3 is a hot spot of aberrations for different types of rearrangement.

Cave:

According to the literature this type of inversion is inherited in balanced condition in about 99% of cases, and can therefore be regarded as carrying no increased genetic risk for the carrier (Fig. 4.36).

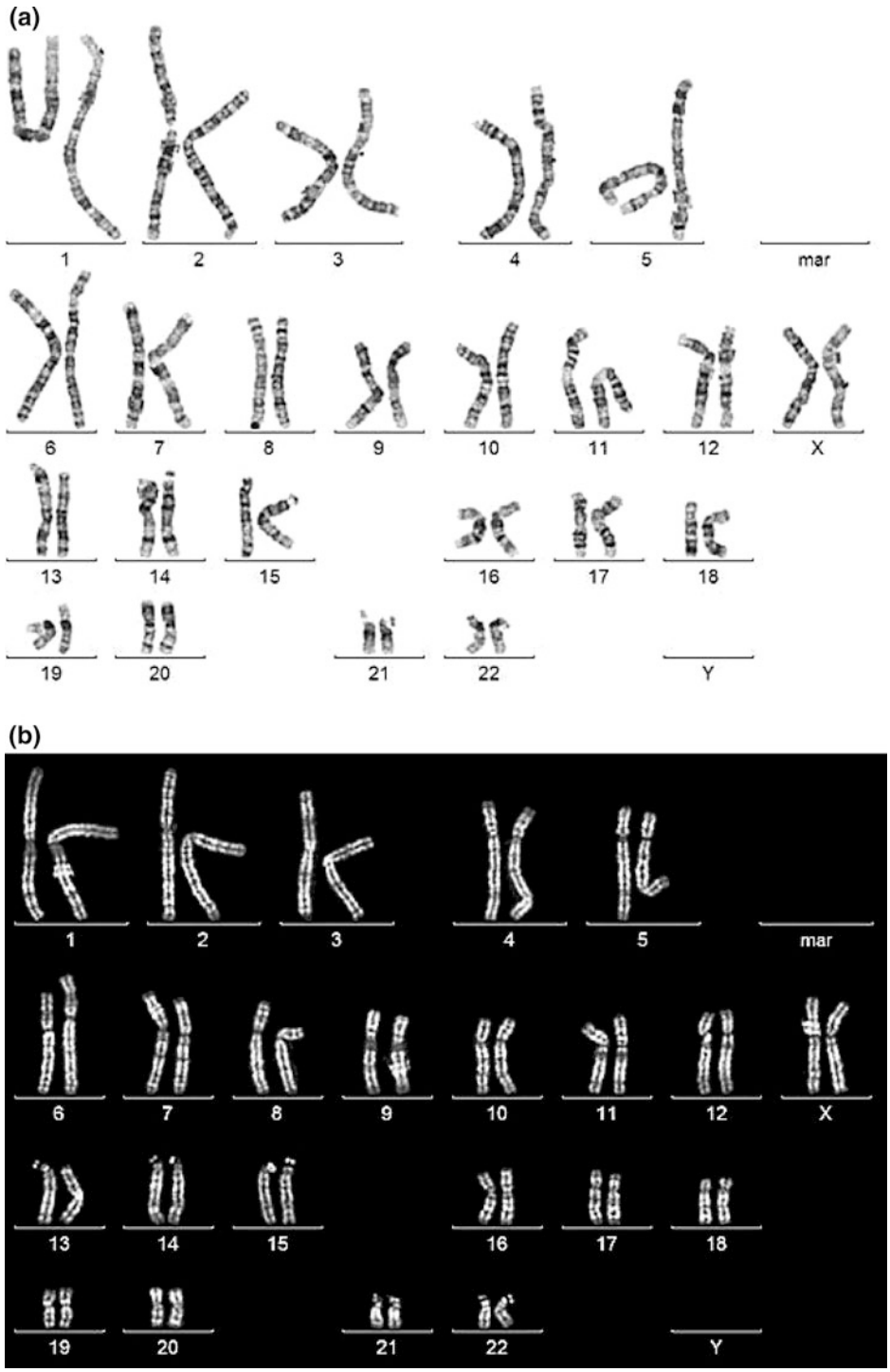

Fig. 4.36 Karyotype 46,XX,inv(15)(q24q26.3). **a** GTG-, **b** QFQ-banding, 700 and 550 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 15, **e** ideograms of chromosome 15, distal position of the inverted segment

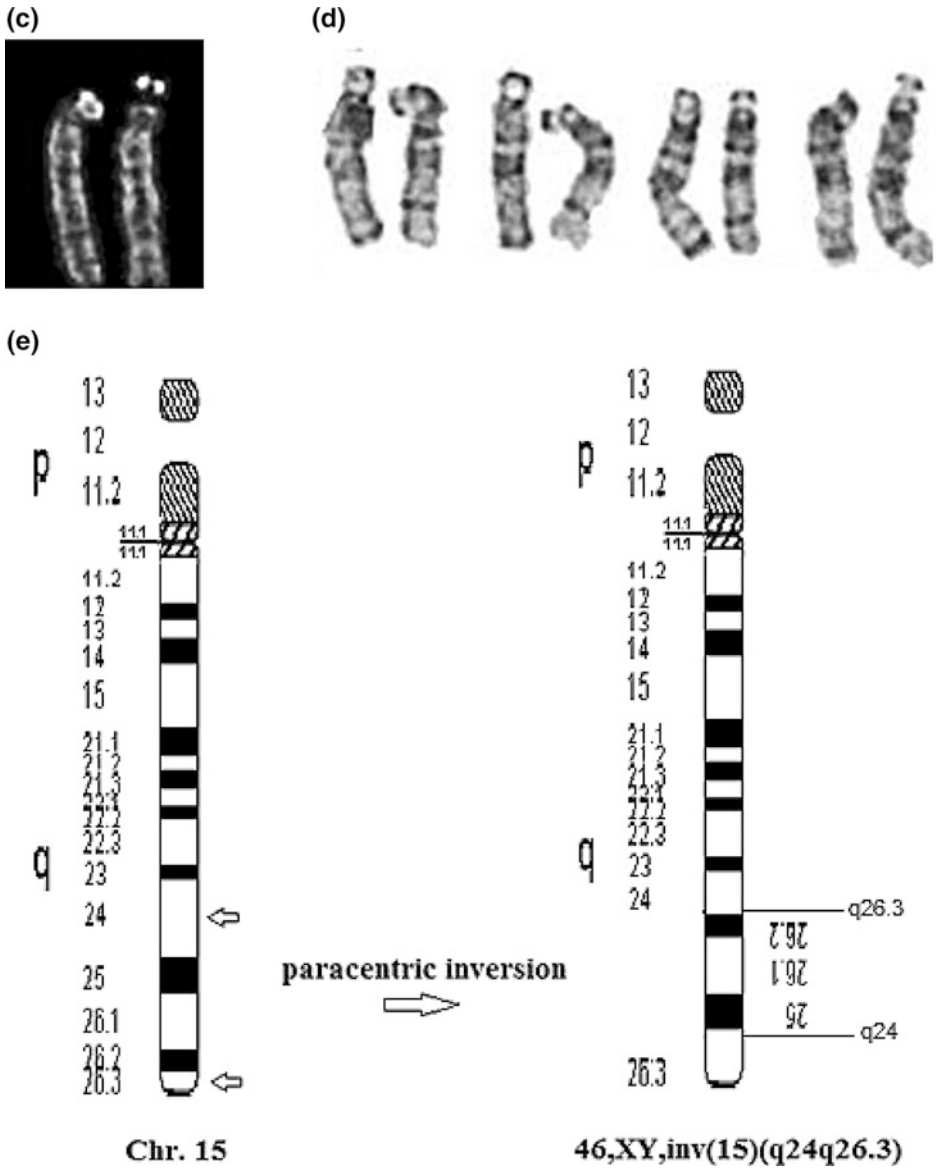

Fig. 4.36 (continued)

Case 37: Karyotype: 46,XY,inv(19)(p12p13.13)

Morphology:

The paracentric inversion in the short arm of chromosome 19 comprises about 15–20% of the total length of the chromosome. The proximal breakpoint is localised in the pericentromeric heterochromatin. The dislocation of this band into a more distal position leads to a striking alteration of the banding pattern. It received a position in an intermediate, GC-rich region. The analysis of this inversion affords a resolution of 700–850 bands per genome.

Cave:

The inverted region is relatively small and the low genetic risk is further reduced by the position of one breakpoint (p12) in a heterochromatic segment (Fig. 4.37).

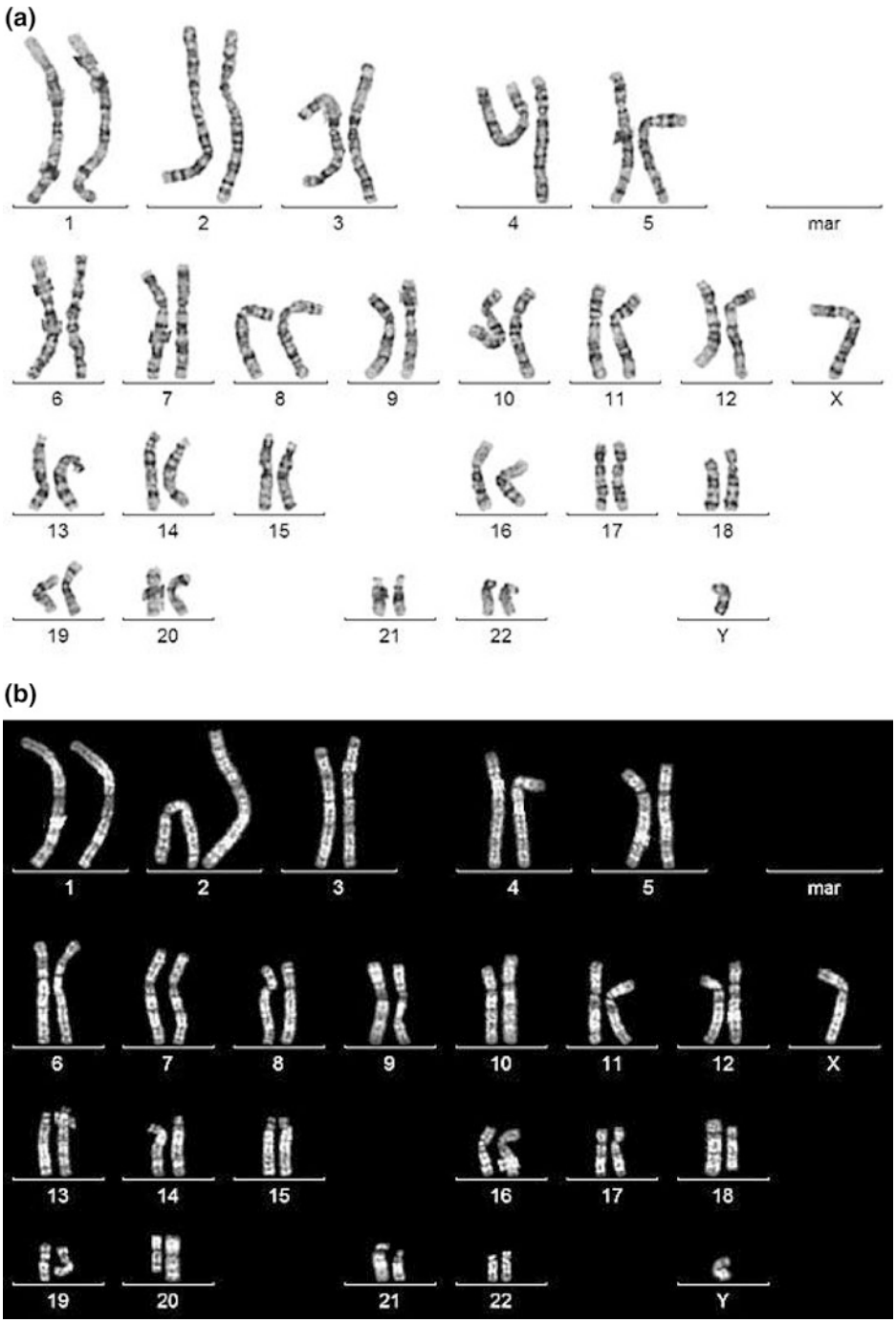

Fig. 4.37 Karyotype 46,XY,inv(19)(p12p13.13). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 19, **f** ideograms of chromosome 19, the inverted chromosome 19 is mainly characterised by the translocation of pericentromeric heterochromatin into the distal short arm

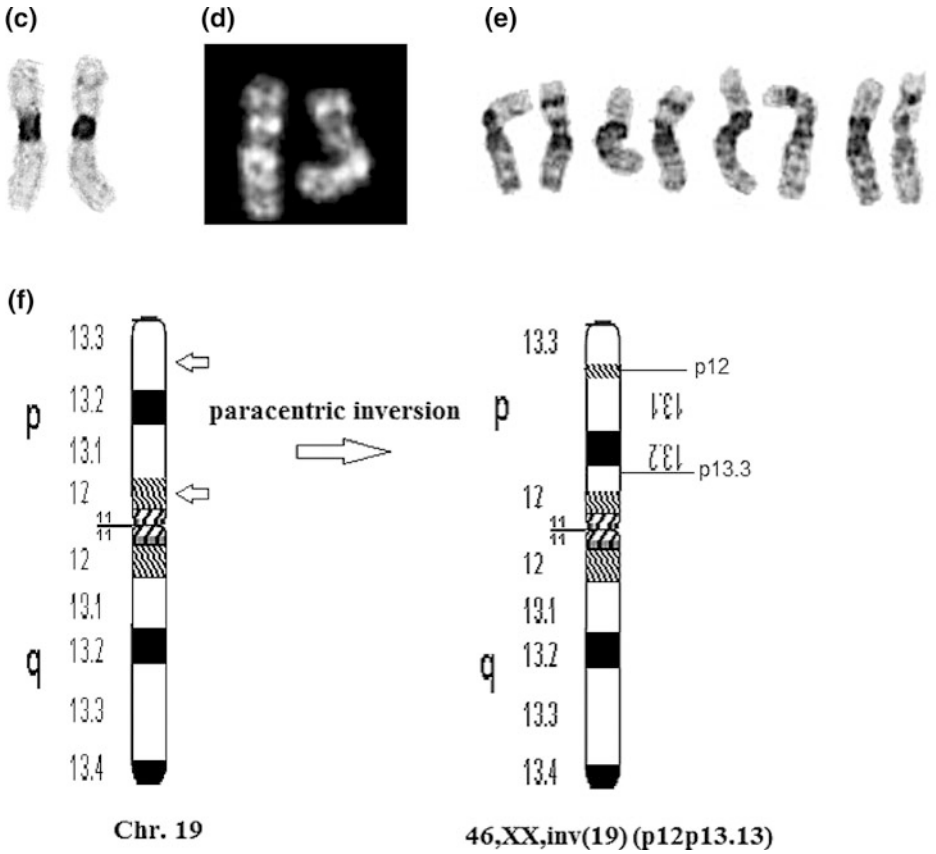

Fig. 4.37 (continued)

Case 38: Karyotype: 46,XX,inv(19)(q13.31q13.42)
Morphology:

A paracentric inversion in the intermediate to distal region of the long arm of chromosome 19 is presented, which comprises about 25% of the total length of the chromosome. The analysis is done by the altered banding pattern, primary by the dislocation of the terminal AT-rich band q13.4 to the more proximal position. This investigation requires a resolution of 700–850 bands per genome.

Cave:

The carrier of this type on inversion should be informed about his low genetic risk (Fig. 4.38).

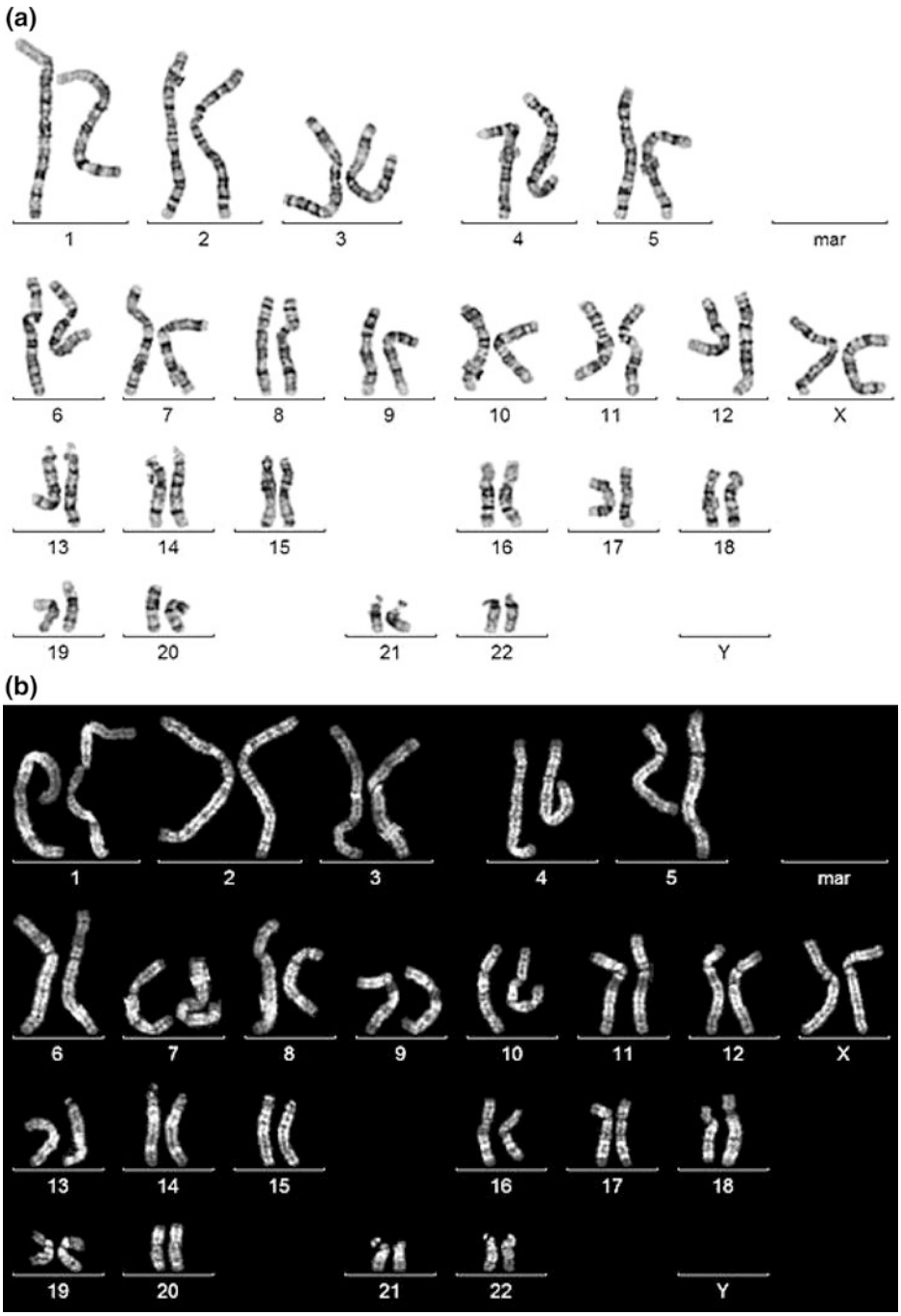

Fig. 4.38 Karyotype 46,XX,inv(19)(q13.31q13.42). **a** GTG-, **b** QFQ-banding, 800 and 700 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted chromosome 19, **e** ideograms of chromosome 19, intermediate inversion in the long arm

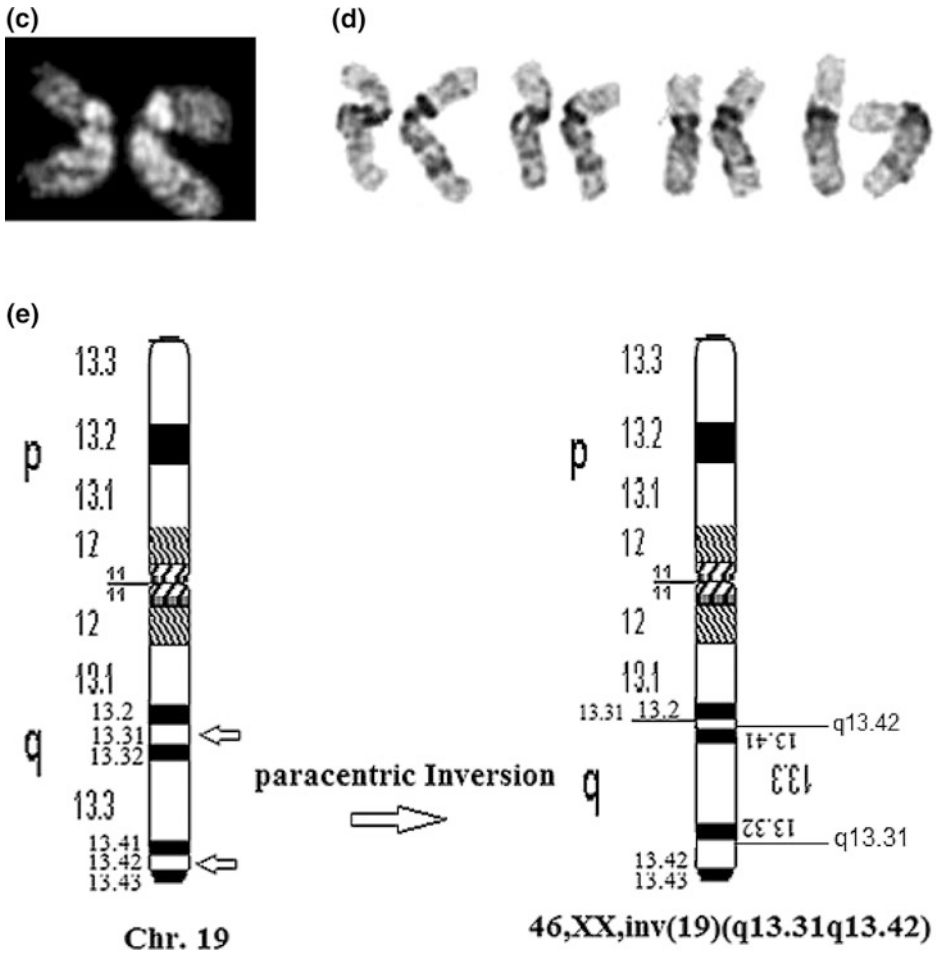

Fig. 4.38 (continued)

Case 39: Karyotype: 46,X,inv(X)(p11.3p22.32)
Morphology:

This is a very characteristic and easy to diagnose inversion, as the main, AT-rich band in the short arm is now located in a more distal position. The length of the inverted segment is about 25% of the total length of the X-chromosome.

Cave:

As the short arm of the X-chromosome is a gene-rich region, prenatal diagnosis is indicated for all inversion carriers, and additionally microarray should be performed, especially in male carriers to exclude unequal crossing over followed by deletion which can be especially relevant in the hemizygotic male (Fig. 4.39).

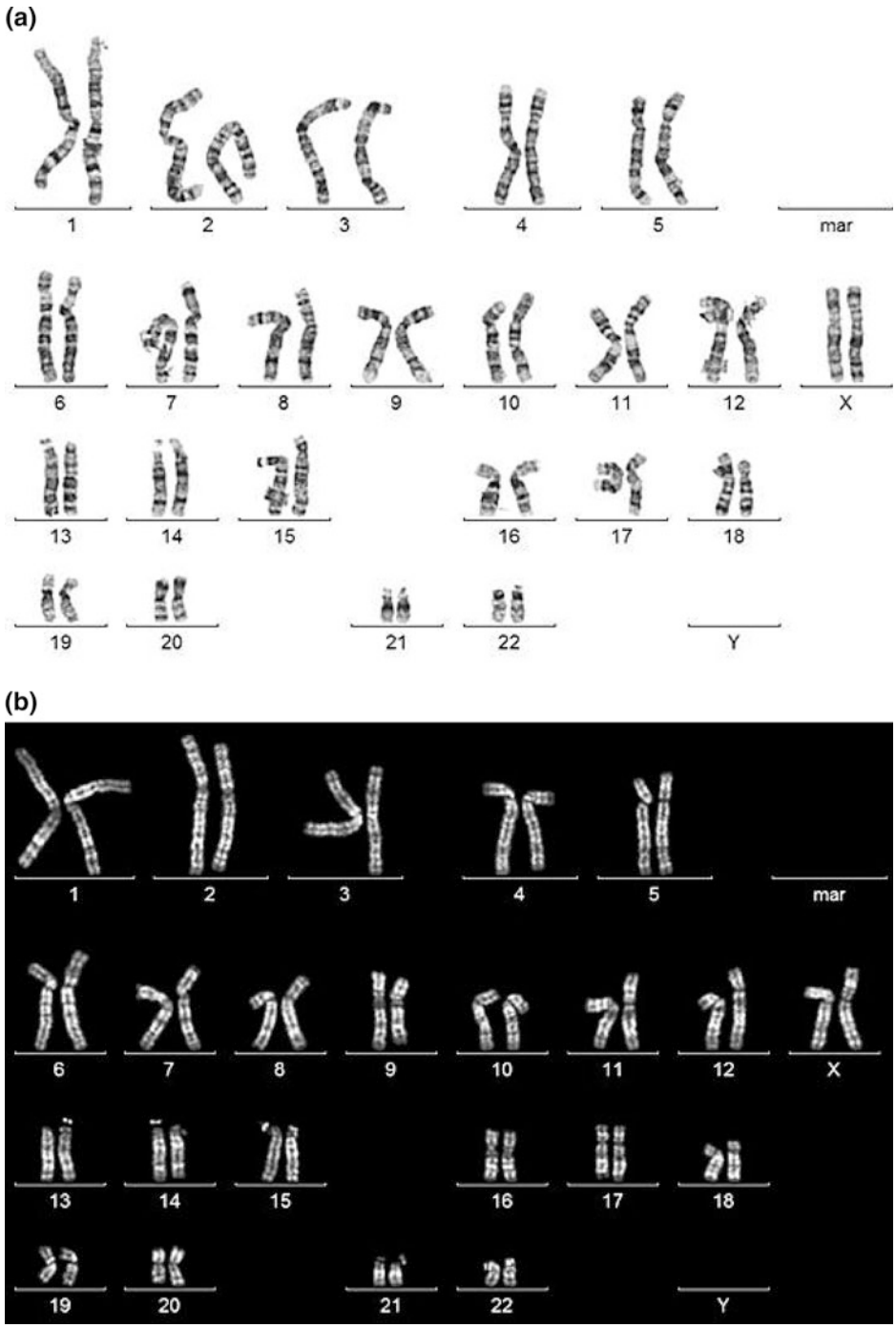

Fig. 4.39 Karyotype 46,X,inv(X)(p11.3p22.32). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* inverted X-chromosome, **e** ideograms of the X-chromosome, inversion comprises almost the total short arm

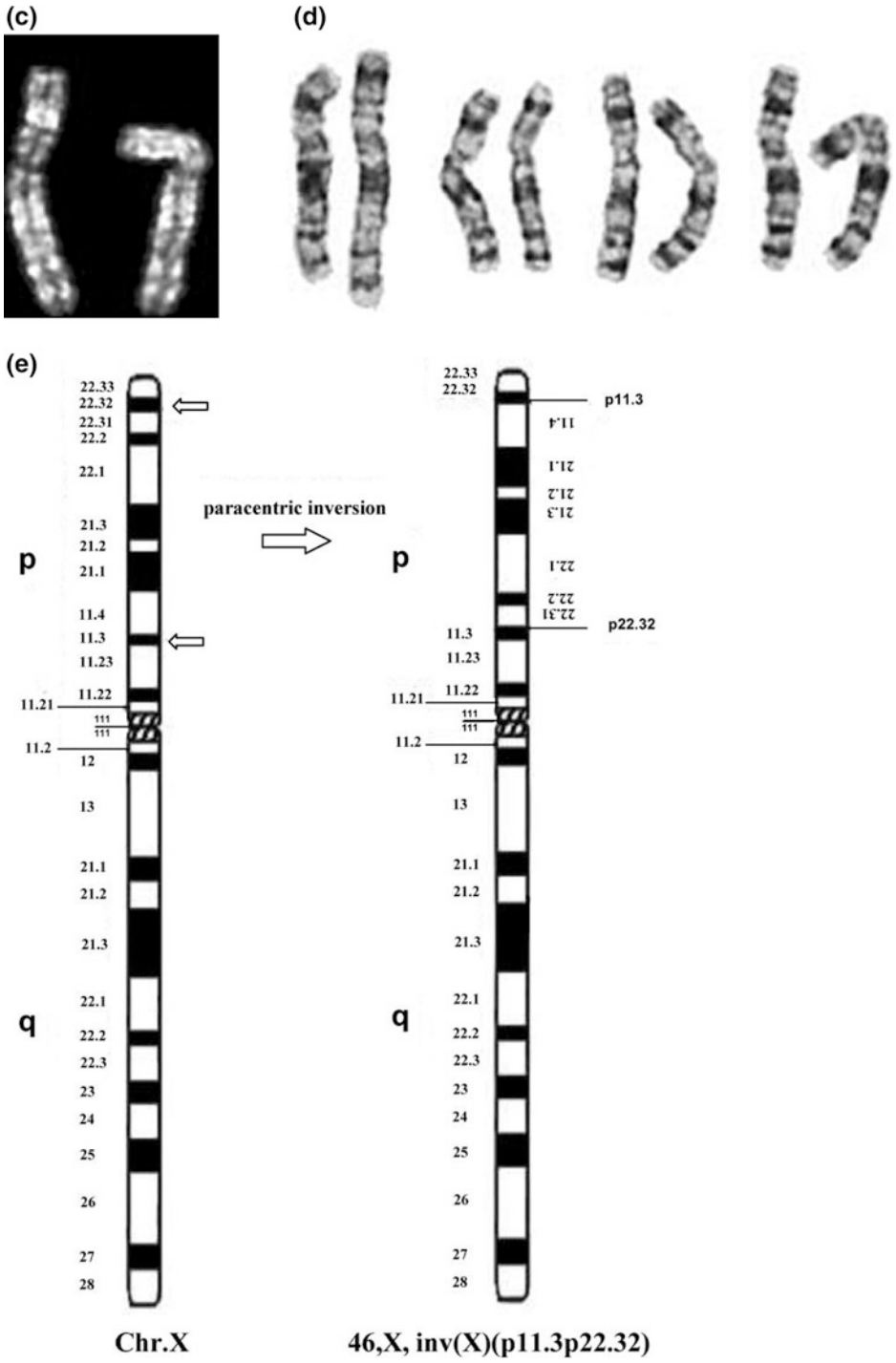

Fig. 4.39 (continued)

Case 40: Karyotype: 46,X,inv(Y)(q11.21q12),inv(9)(p12q12),inv(9)(p12q13)

The proband has three different inversions, two of them in heterochromatic regions and one in euchromatin and heterochromatin.

Morphology:

1. inv (Y)(q11.21q12)
   The paracentric inversion in the long arm has one breakpoint in the proximal AT-rich band q11.21 and the second one in the heterochromatic block q12. The segment comprises about 45% of the total length of the Y-chromosome, which is an individual percentage, as the length of q12 is very variable. The analysis of the inversion is performed by a combination of GTG, QFQ, and CBG-banding, as the distal heterochromatic block is dislocated and the banding pattern in the euchromatin has changed. The aberration is easy to recognize, but the breakpoint determination affords a resolution of at least 550 bands per genome.

2.+3. inv(9)(p12q13): Type I and inv(9)(p12q12): Type II
   Both chromosomes 9 show, classified as heteromorphisms or variants, pericentric inversions of the heterochromatin. Whereas one of them presents with a complete inversion of the heterochromatic block q12 (Type I, frequency in the European population 1%) the second one shows a partial inversion (Type II, frequency in the European population 10%).

Cave:

The heterochromatin inversions of chromosome 9 present with no increased genetic risk. The paracentric inversion Y can cause male fertility problems (Fig. 4.40).

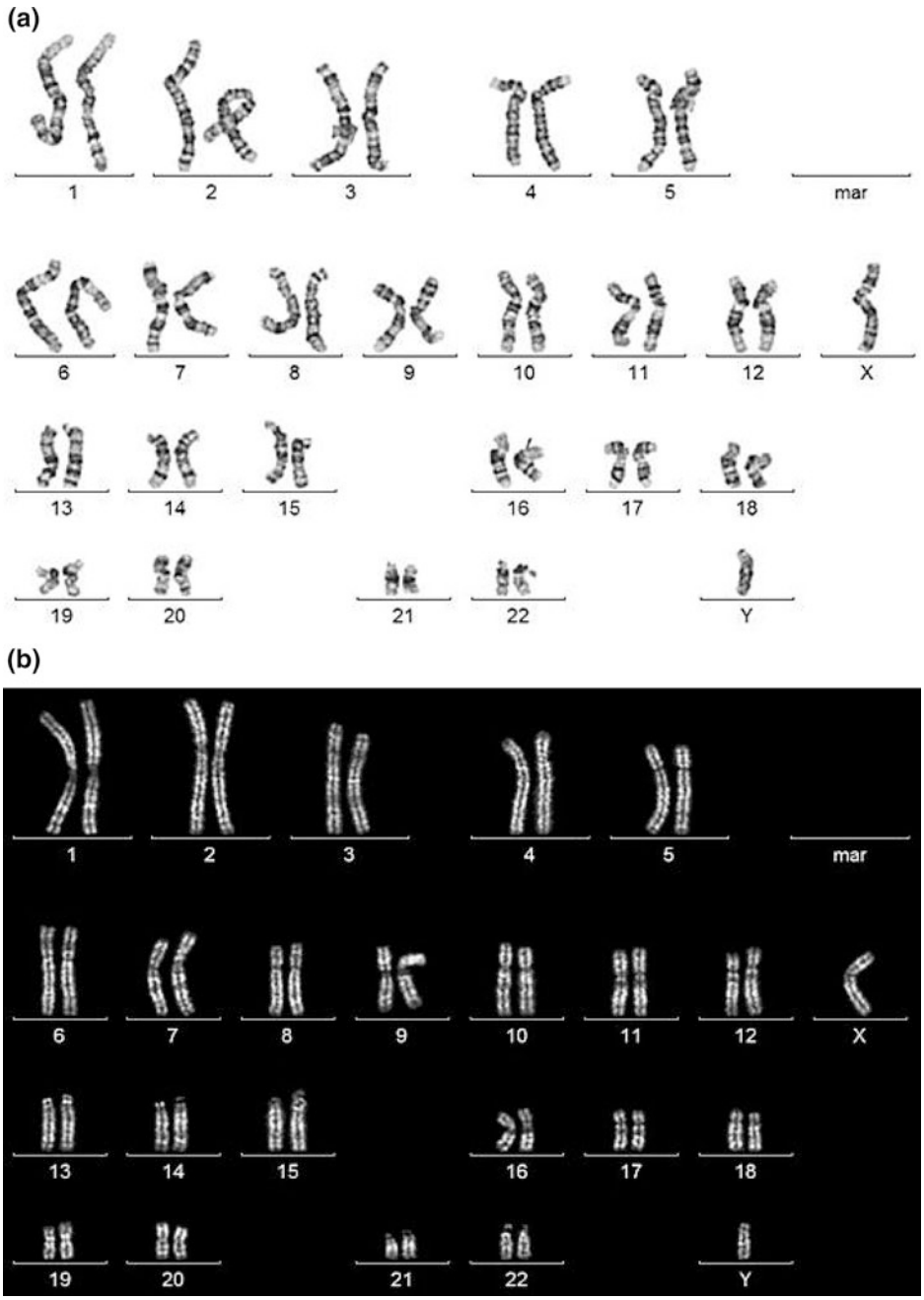

Fig. 4.40 Karyotype 46,X,inv(Y)(q11.21q12),inv(9)(p12q12),inv(9)(p12q13). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, d/1: Y-chromosome from a normal control person, **f** ideograms of the Y-chromosome, one breakpoint in the constitutive heterochromatin, **g** ideograms of a normal (control person) and two inverted chromosome 9, all breakpoints in the constitutive heterochromatin

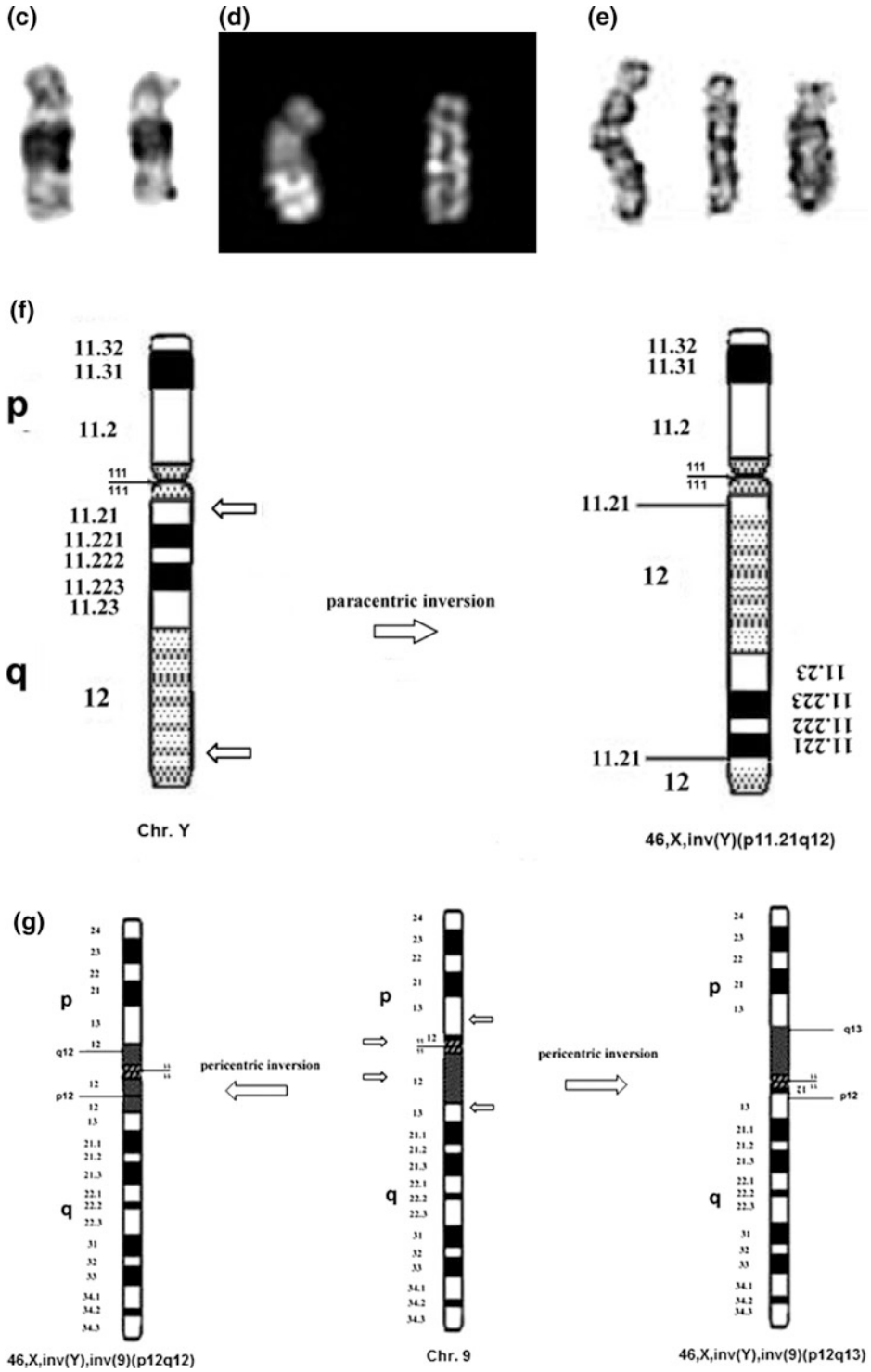

Fig. 4.40 (continued)

Summary

The collection presented here includes 47 inversions. For reasons of space only 40 were described in detail. The total investigations group comprises paracentric and pericentric inversions in frequencies of 58 and 42%, which means that paracentric inversions were more frequent than pericentric ones in the investigation group. Furthermore an unequal interchromosomal distribution of the chromosomes involved was noted: the large chromosomes 1–12 and the X-chromosome showed 73% of the inversions, chromosomes 13–22 and Y only 27%, and in the latter group chromosomes 17, 18, 21 and 22 showed no inversions at all.

In pericentric inversions the breakpoints were approximately uniformly distributed in proximal, intermediate, and distal chromosome regions, whereas in paracentric inversions about 52% were located intermediate, 33% distal and only 15% proximal.

The size of the inverted regions ranges from 4% to a maximum of 80% of the total length of the chromosome involved.

All inversions shown could be safely distinguished by the altered banding pattern from insertions.

4.2.1.2 Deletions

1 46,XY,del(1)(p36.3)
2 46,XY,del(2)(q31q32.1),inv(4)(p12q11.2)
3 46,XY,del(4)(q31.3)
4 46,XX,del(5)(p14.2)
5 46,XX,del(5)(p15.1)
6 46,XY,del(8)(p23) [40]/46,XY[1]
7 46,XX,del(9)(p22p24),inv(4)(p12q11.2)
8 46,XX,del(10)(p13p15.1)
9 46,XY,del(13)(q21.2q31)
10 46,XY,del(15)(q11.2q13),inv4(p12q11.2)
11 46,XY,del(17)(p11.2),inv4(p12q11.2)
12 46,XX,del(17)(q23.1q23.3)
13 46,XX,del(18)(p11.2)dup(7)(q36)t der(18),t(7;18)(q36;p11.2)(D18S552-,7QTEL20 +),inv(9)(p12q13)
14 46,XX,del(18)(q21.3),inv(4)(p12q11.2)
15 46,X,del(X)(p11.23)
16 46,X,del(X)(p22.1)
17 46,X,del(X)(p22.1p22.2),inv(4)(p12q11.2)
18 46,X,del(X)(q21.2)
19 46,X,del(X)(q27.2)
20 46,X,del(Y)(q11.22)

Case 1: Karyotype: 46,XY,del(1)(p36.3)

Indication for chromosome analysis: Characteristic symptoms of the deletion 1p36

Morphology:

The deleted chromosome ends with the AT-band p36.2. A resolution of 550–700 bands per genome is necessary, to get a precise diagnosis in the case presented here.

Cave:

Chromosome investigations in the parents should be performed to exclude the presence of a balanced reciprocal translocation in one of them. After these additional analyses a summarizing genetic counselling should be offered to them (Fig. 4.41).

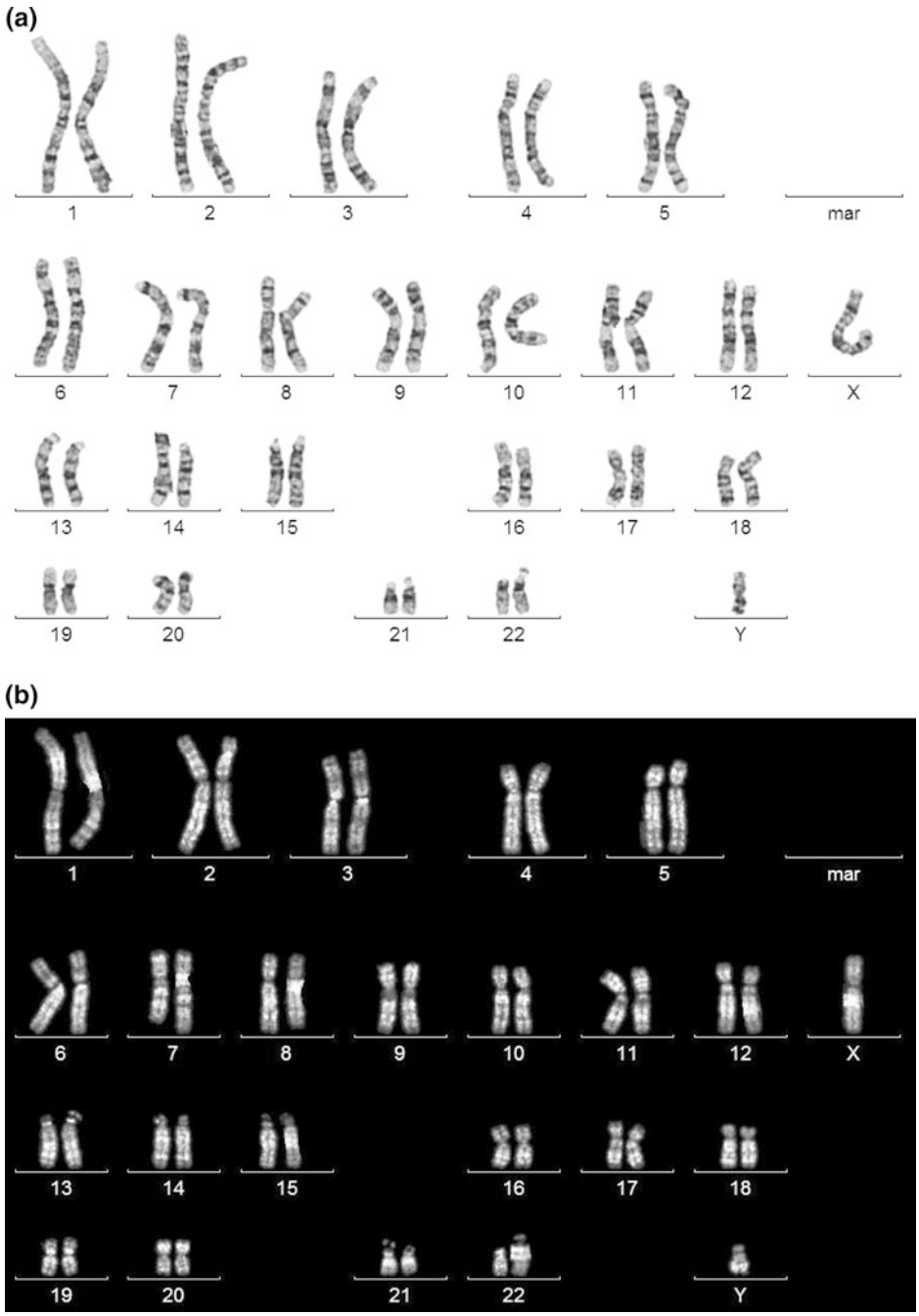

Fig. 4.41 Karyotype 46,XY,del(1)(p36.3). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 1, **e** ideograms of chromosome 1, small distal deletion in the short arm

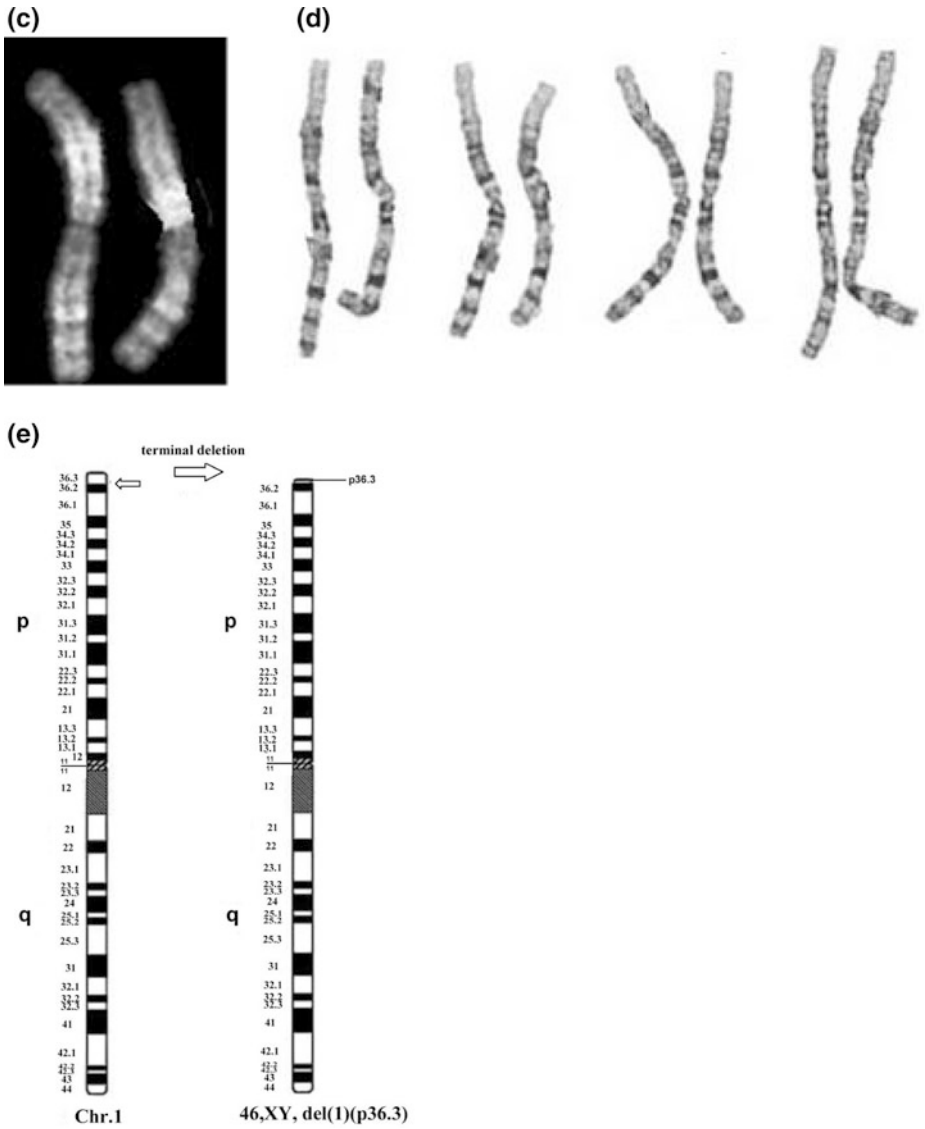

Fig. 4.41 (continued)

Case 2: Karyotype: 46,XY,del(2)(q31q32.1),inv(4)(p12q11.2)

The proband shows a euchromatic deletion and a pericentromeric inversion in the heterochromatin block of chromosome 4.

Indication for chromosome analysis: Developmental retardation.

Morphology:

1. del(2)(q31q32.1)
   The interstitial deletion in the long arm of chromosome 2 leads to an altered banding pattern and to a change in the index of long and short arm.
2. inv(4)(p12q11.2)
   This inversion involves only heterochromatic segments and is therefore classified as polymorphism without genetic relevance. In the European population it is the most frequent inversion in a heterochromatic region with 7.6%.

Cave:

The parents must be investigated to exclude a paracentric inversion in one of them. Genetic counseling is indicated (Fig. 4.42).

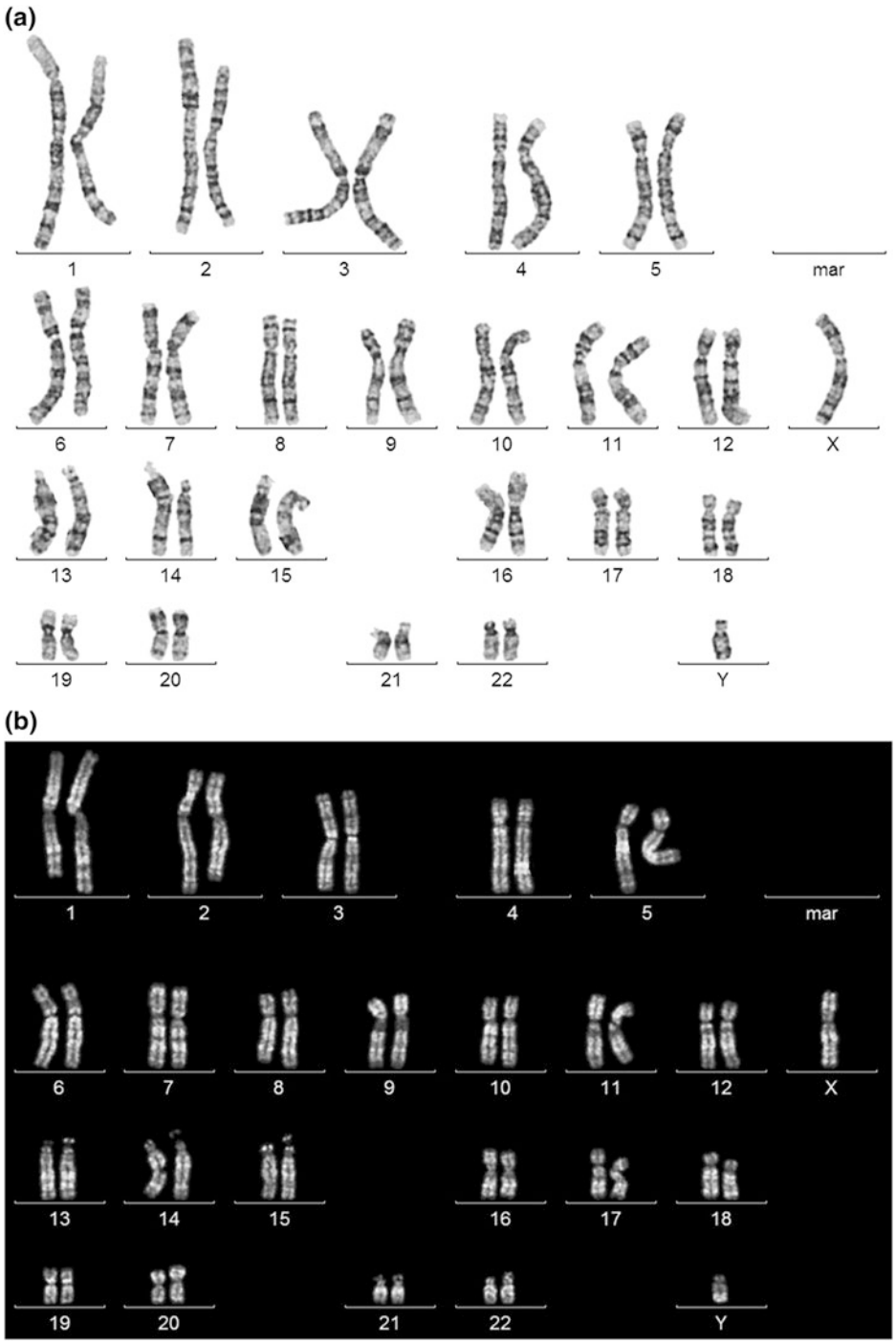

Fig. 4.42 Karyotype 46,XY,del(2)(q31q32.1),inv(4)(p12q11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 2, **e** *left* normal, *right* inverted chromosome 4, **f** ideograms of chromosome 2, short interstitial deletion in the long arm, **g** ideograms of chromosome 4, pericentric inversion restricted to the pericentromeric heterochromatin

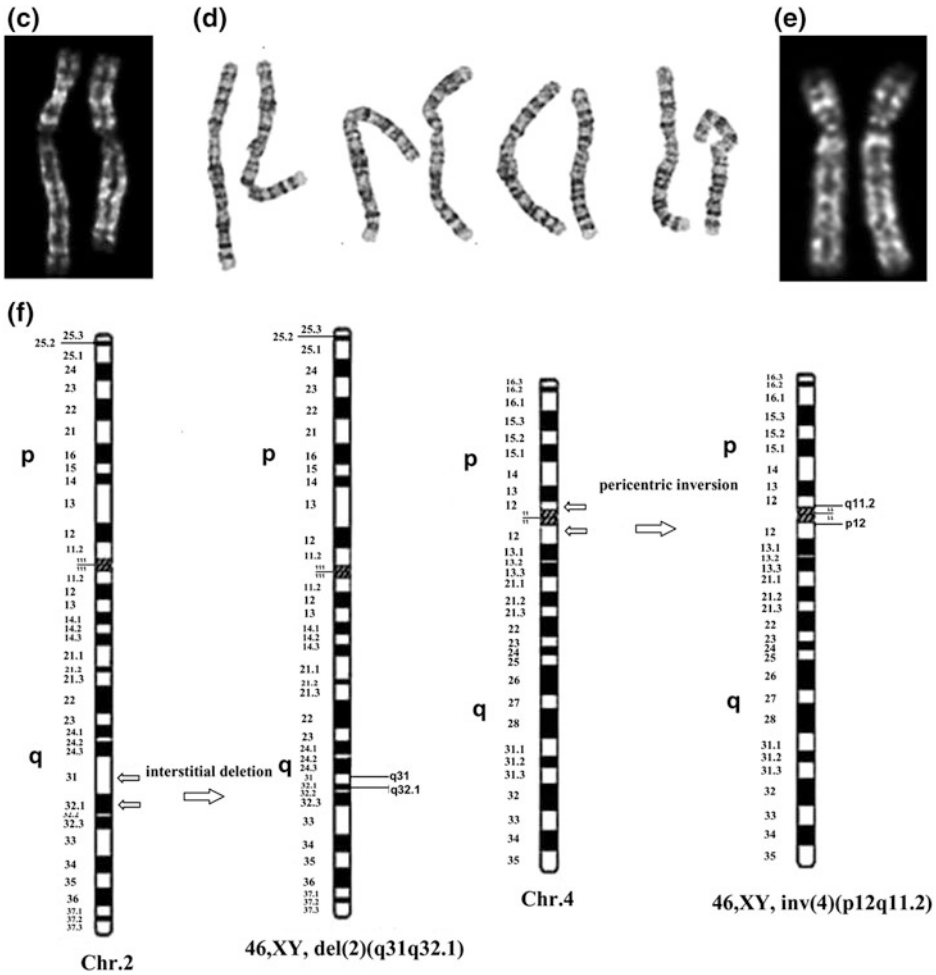

Fig. 4.42 (continued)

Case 3: Karyotype: 46,XY,del(4)(q31.3)

Indication for chromosome analysis: Characteristic clinical symptoms of the deletion syndrome 4q31.

Morphology:

The long arm of the deleted chromosome has only about 70% of its original length left.

Cave:

The chromosomes of the parents should be investigated to exclude a reciprocal translocation in one of them and thereafter genetic counseling should be offered (Fig. 4.43).

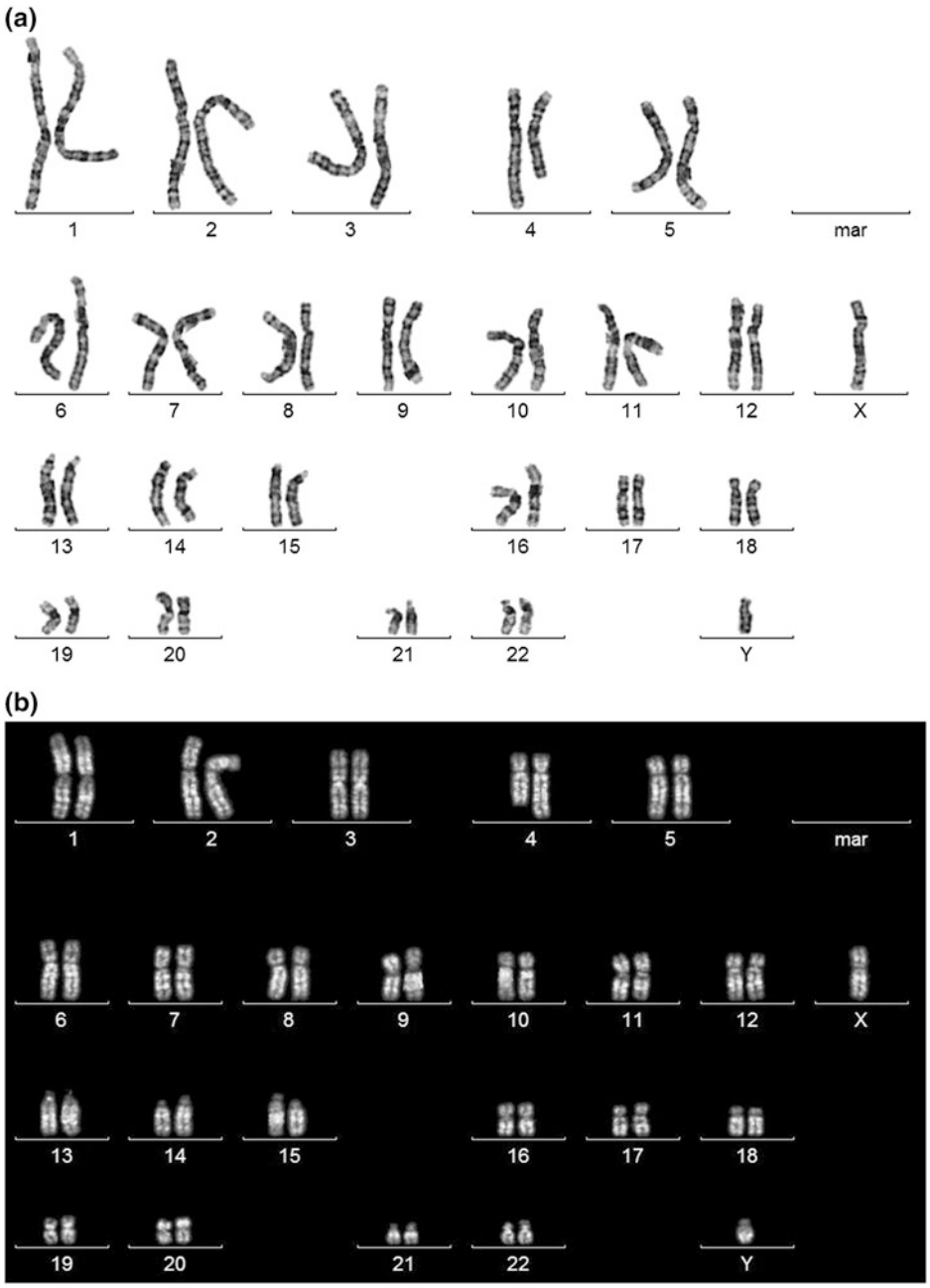

Fig. 4.43 Karyotype 46,XY,del(4)(q31.3). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 4, **e** ideograms of chromosome 4, deletion distal in the long arm

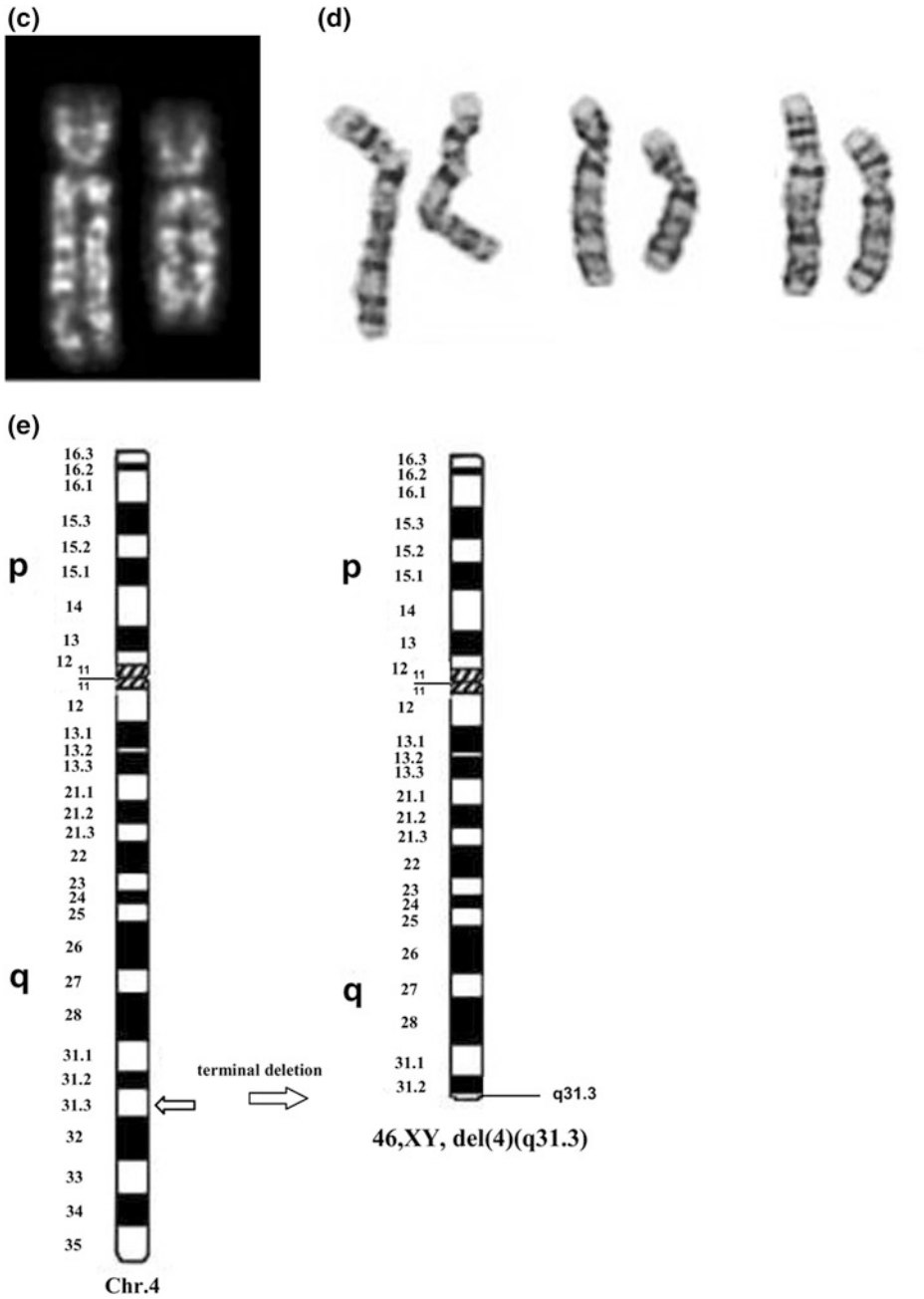

Fig. 4.43 (continued)

Case 4: Karyotype: 46,XX,del(5)(p14.2)

Indication for chromosome analysis: Cri-du-chat syndrome with typical crying, characteristic facial features and moderate retardation.

Morphology:

The deletion of the patient comprises about 50% of the short arm of chromosome 5.

Cave:

In about 8–15% of the cases the deletion 5p originated from the inheritance of an unbalanced translocation of parental origin. Therefore the chromosomes of the parents should be investigated to enable a realistic risk estimation (Fig. 4.44).

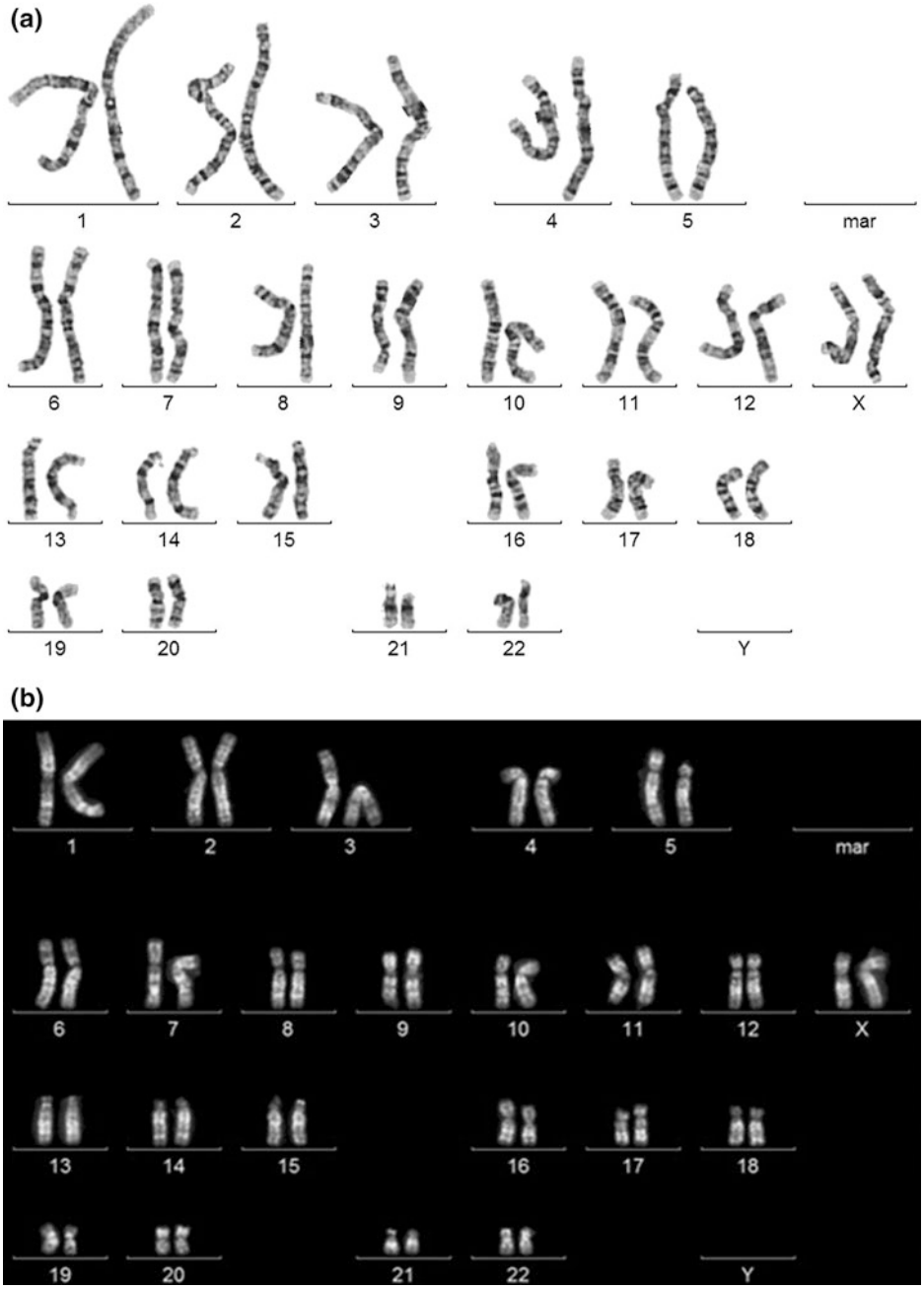

Fig. 4.44 Karyotype 46,XX,del(5)(p14.2). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 5, **e** ideograms of chromosome 5. Terminal deletion of about 50% of the short arm

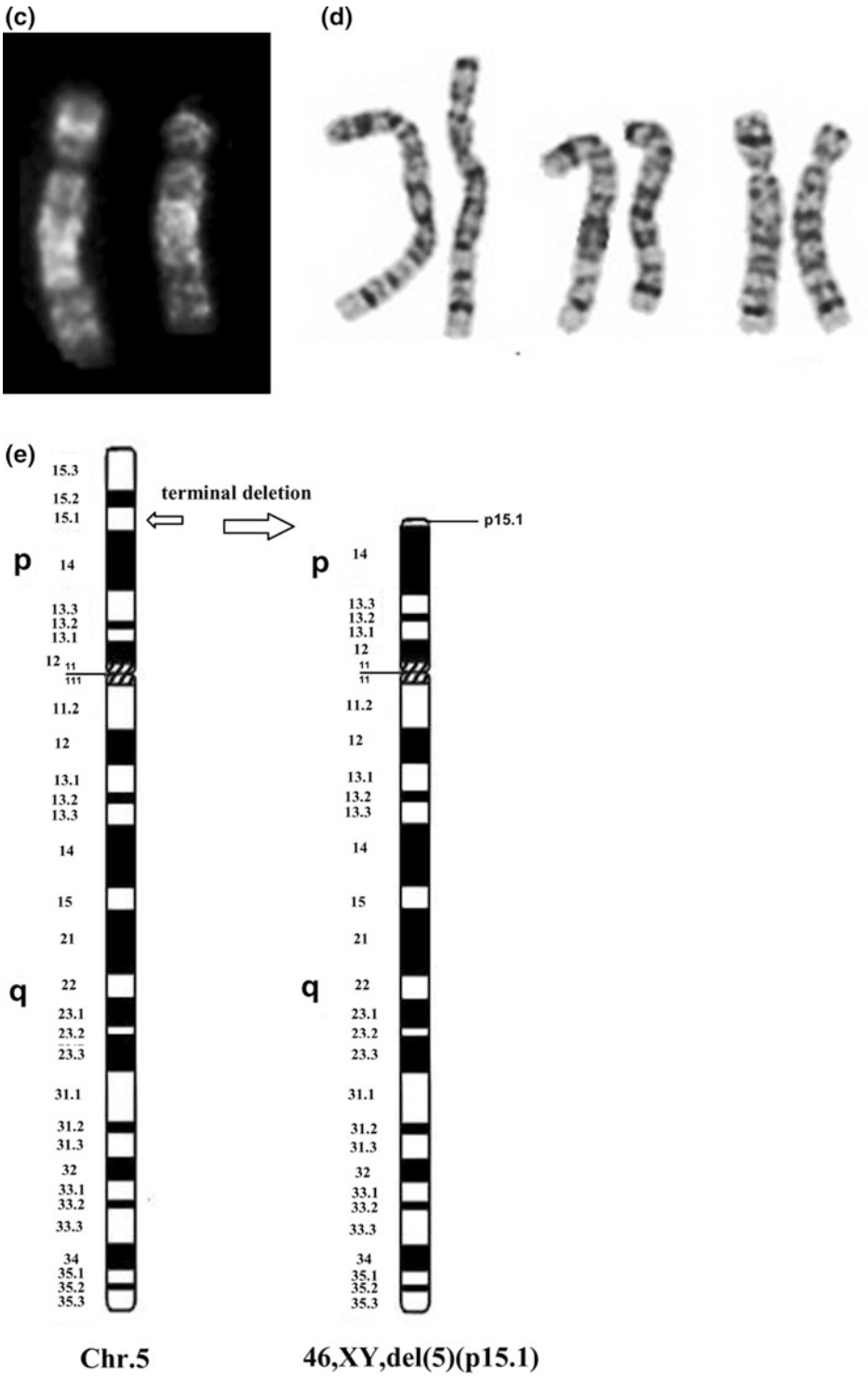

Fig. 4.44 (continued)

Case 5: Karyotype: 46,XX,del(5)(p15.1)

Indication for chromosome analysis: Typical crying of children with Cri-du-chat syndrome, but not typical facial features, mild to moderate retardation.

Morphology:

The deletion shows a more distal breakpoint than in the previous case 4 which is the reason for the less severe phenotype in the patient. In both cases (4 and 5) the banding resolution has to be at least 550 bands per genome. Otherwise the breakpoints cannot be determined safely. But this is relevant for a prognosis of development.

Cave:

The same criteria have to be taken into account as in case 4 (Fig. 4.45).

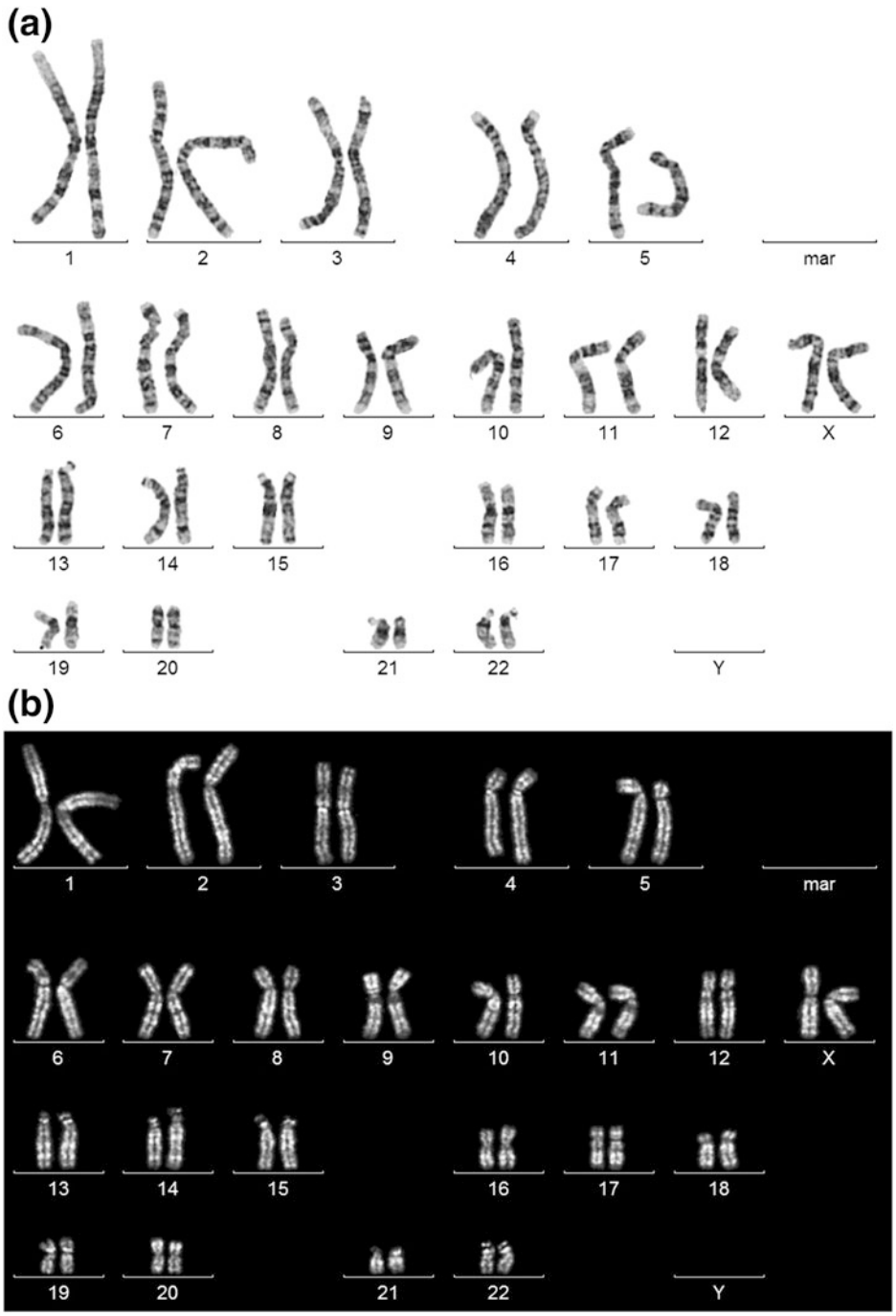

Fig. 4.45 Karyotype 46,XX,del(5)(p15.1). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, **c** *left* normal, *right* deleted chromosome 5, **e** ideograms of chromosome 5. Terminal deletion of the short arm

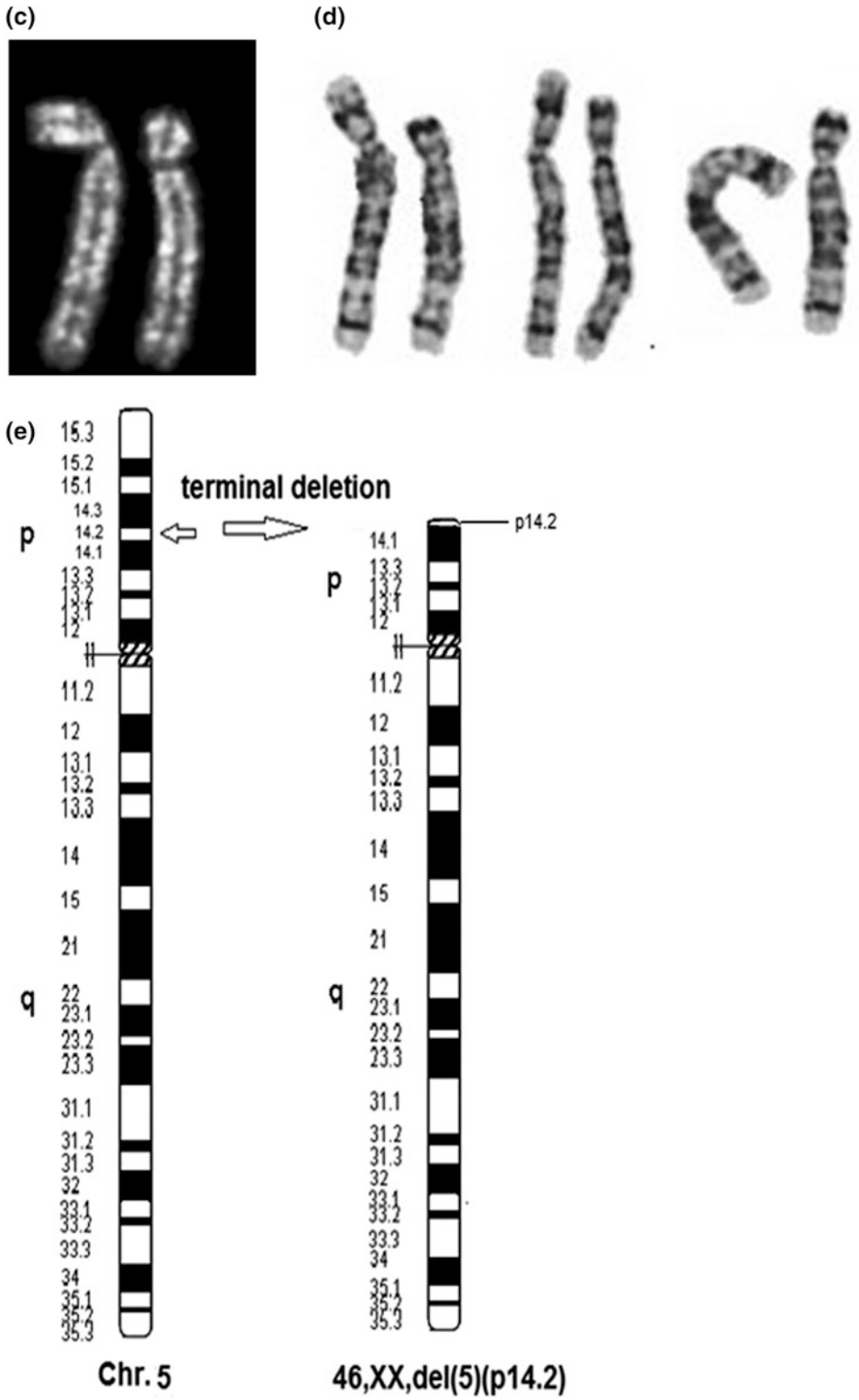

Fig. 4.45 (continued)

Case 6: Karyotype: mos46,XY,del(8)(p23) [40]/46,XY[1]

Indication for chromosome analysis: Pathologic course of pregnancy, spontaneous abortion first trimenon.

Morphology:

The chromosome analysis is based on a chorionic villus sample. Therefore the banding resolution is reduced. The distal deletion in the short arm of chromosome 8 presents as mosaic. Therefore the deletion must be of postzygotic origin caused

by an abnormality in the course of the cell cycle and it originated in the pathologic conceptus de novo. As the analysis was performed on a biopsy of the abortion material quantitative analyses of the two karyotypes were not possible as well as their distribution in different cell systems.

Cave:

This case makes it obvious, that chromosome investigations always afford the analysis of a sufficient number of mitoses. Additional microarray analyses will not provide the investigator with further informations (Fig. 4.46).

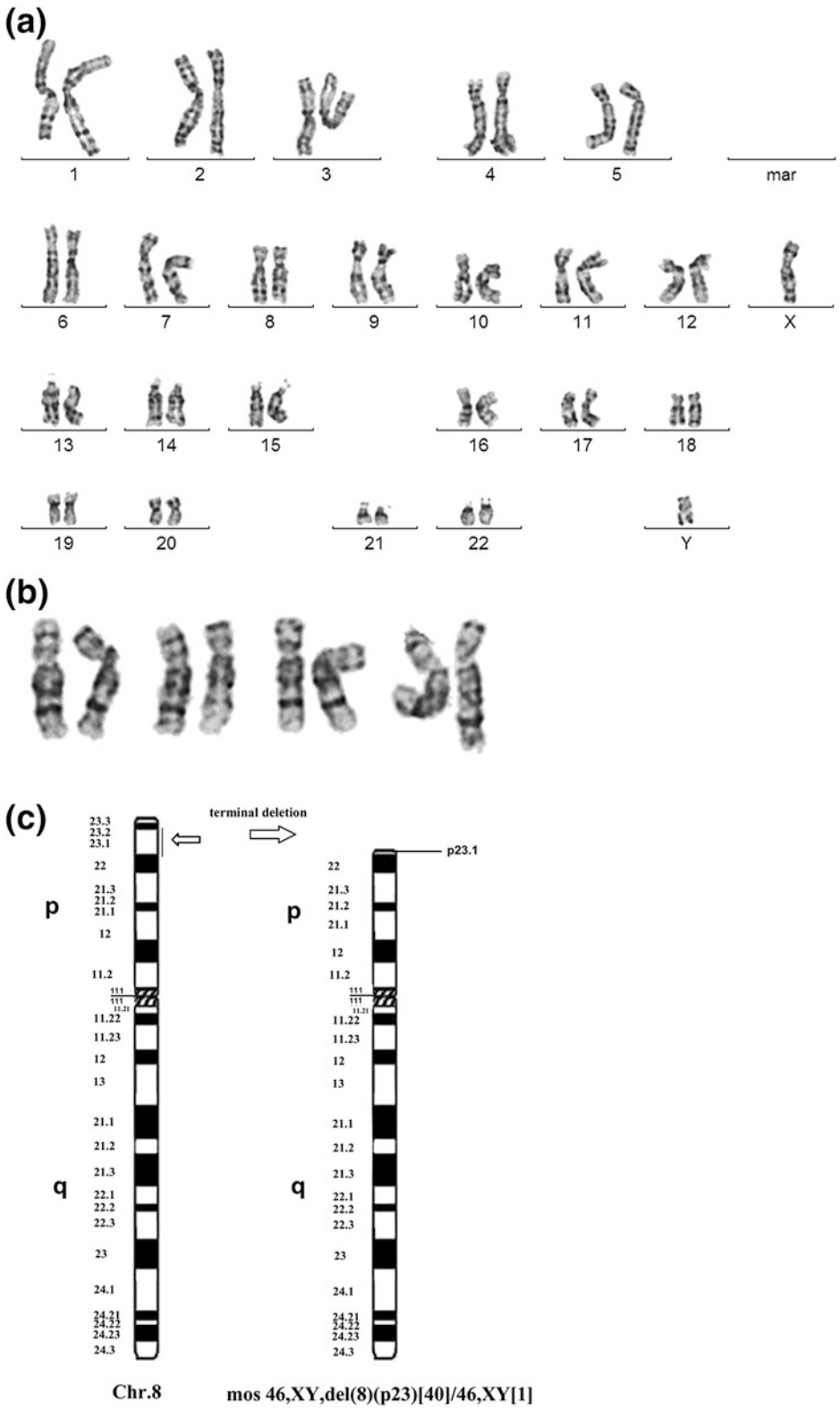

Fig. 4.46 Karyotype mos 46XY, del(8)(p23)/46XY. **a** GTG-banding: 550 bands per genome, **b** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 8, **c** ideograms of chromosome 8, small terminal deletion of the short arm

Case 7: Karyotype: 46,XX,del(9)(p22p24),inv(4)(p12q11.2)

Two rearrangements are diagnosed, one in the euchromatin and the second in the constitutive heterochromatin.

Indication for chromosome analysis: Developmental retardation.

Morphology:

1. del(9)(p22p24)
   The interstitial deletion in the short arm comprises about 10% of the total length of chromosome 9 and about 40% of the short arm. The centromere shows a more acrocentric position and the banding pattern in the short arm has changed, thus the analysis is easy to perform. But the breakpoint localisation requires a resolution of about 550 bands per genome.
2. inv(4)(p12q11.2)
   See: Case 2.

Cave:

The chromosomes of the parents must be analysed before genetic counseling to exclude a parental paracentric inversion (Fig. 4.47).

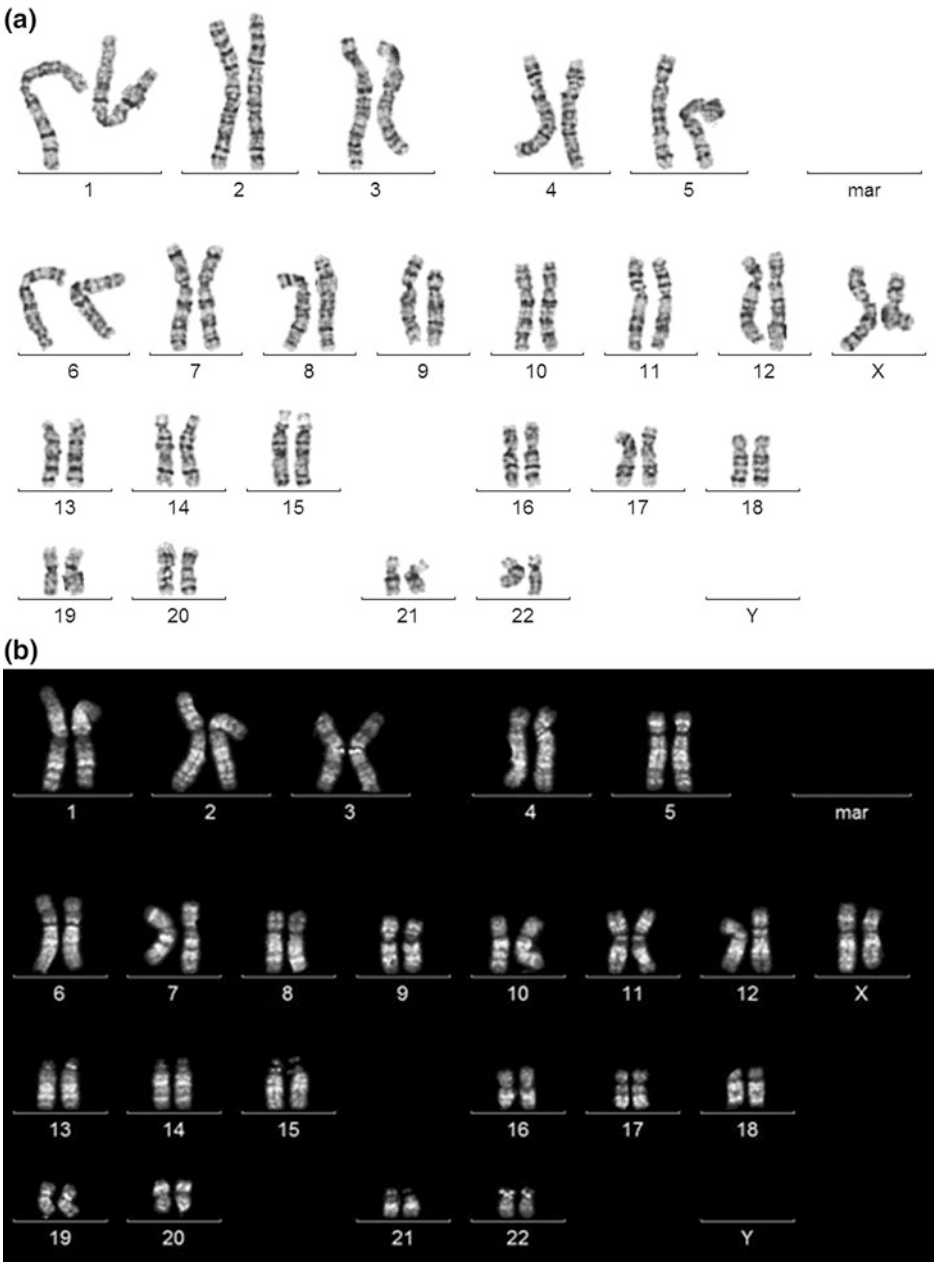

Fig. 4.47 Karyotype 46,XX,del(9)(p22p24),inv(4)(p12q11.2). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 9, inv(4) see Case 2, **d** ideograms of chromosome 9. Terminal deletion in the short arm, inv(4) see Case 2

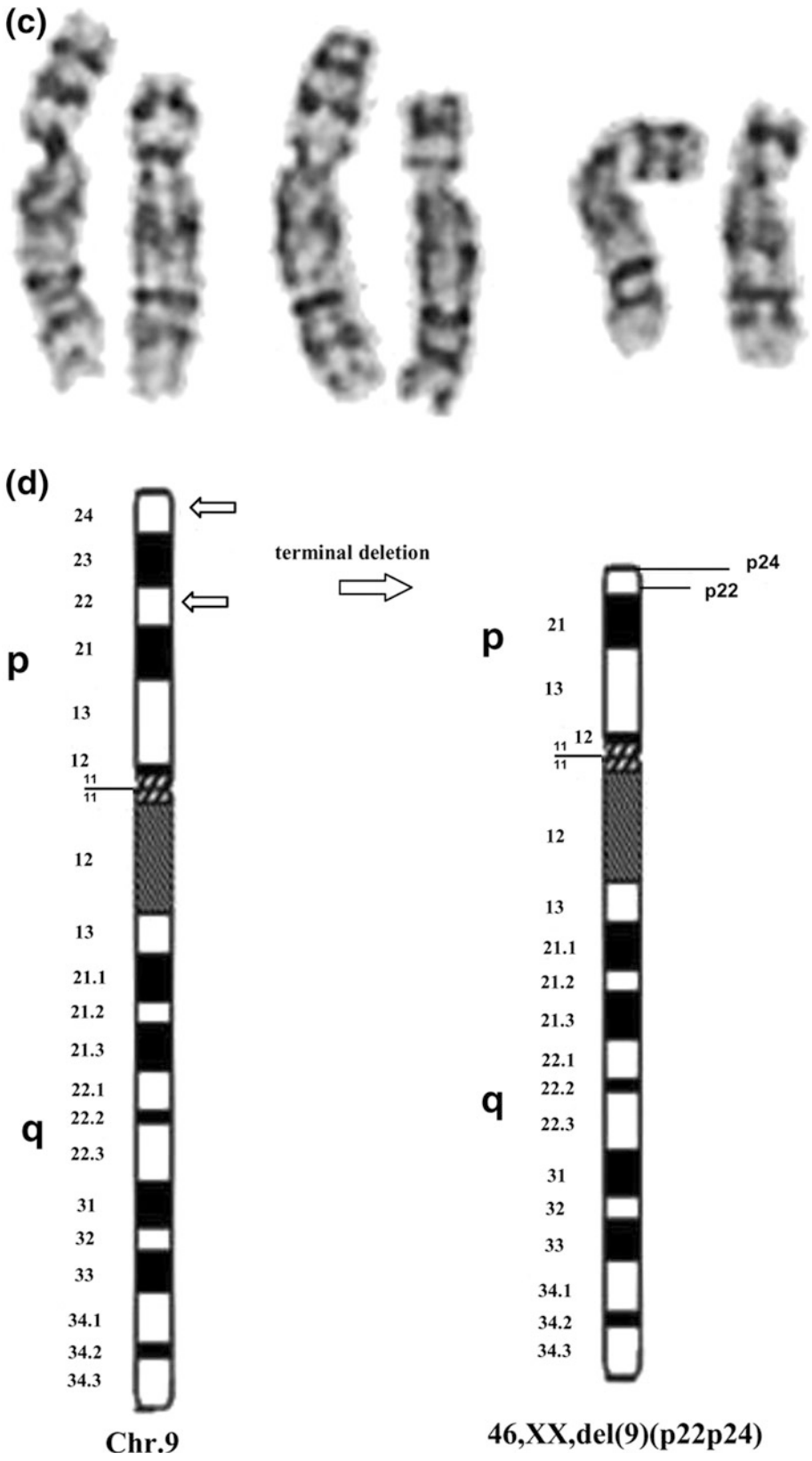

Fig. 4.47 (continued)

Case 8: Karyotype: 46,XX,del(10)(p13p15.1)
Indication for chromosome analysis: Developmental retardation.

Morphology:

The interstitial deletion in the short arm of chromosome 10 includes the AT-rich band p14 and is therefore easy to diagnose.

Cave:

Family investigations should be performed before the genetic counseling to exclude a parental inversion (Fig. 4.48).

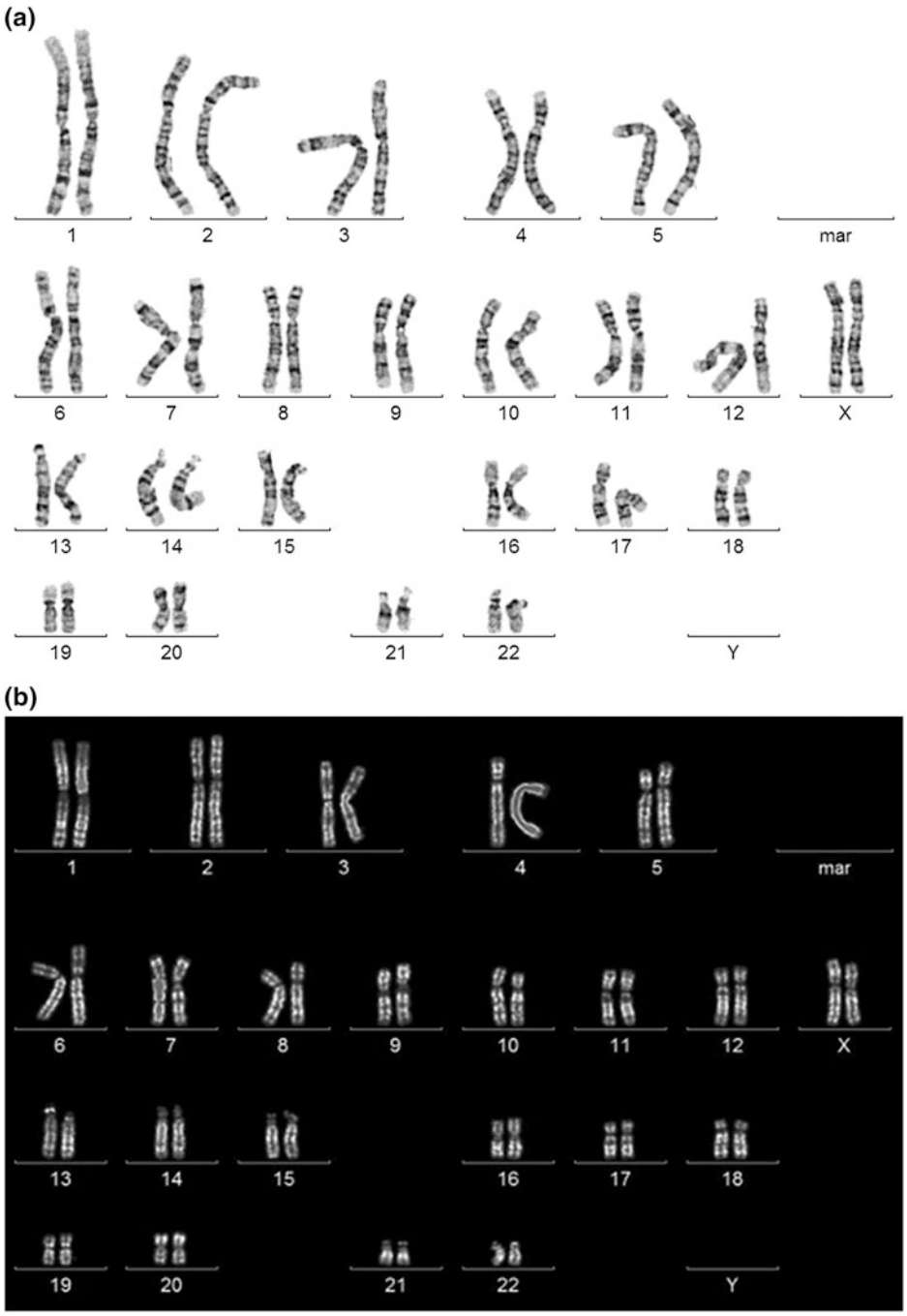

Fig. 4.48 Karyotype 46,XX,del(10)(p13p15.1). **a** GTG-, **b** QFQ-banding, 600 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 10, **e** ideograms of the chromosome 10, interstitial deletion in the short arm

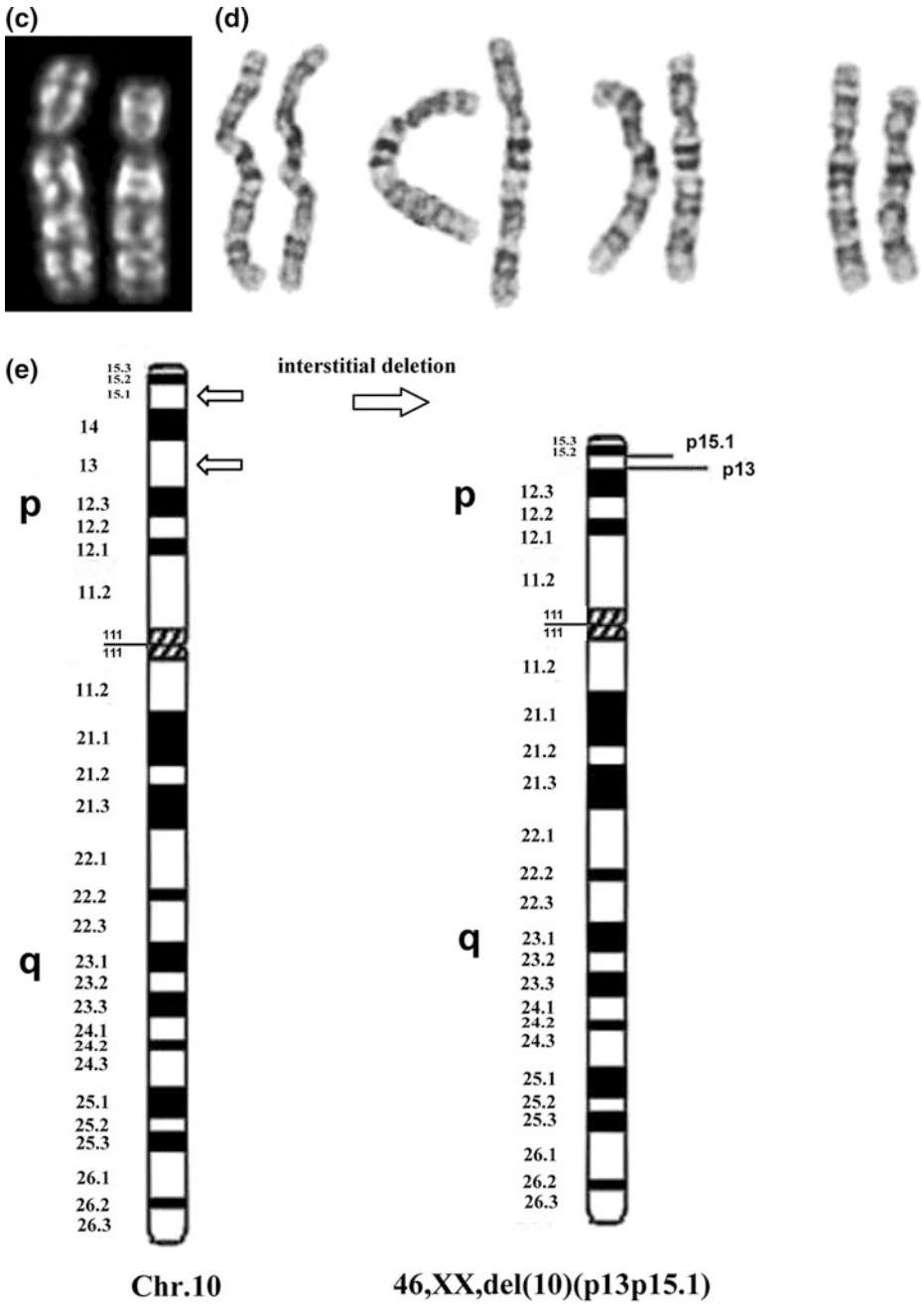

Fig. 4.48 (continued)

Case 9: Karyotype: 46,XY,del(13)(q21.2q31)

Indication for chromosome analysis: Multiple malformations. The pattern of clinical symptoms is in accordance with findings from the literature in cases of similar deletions. The prognosis is unfavorable.

Morphology:

The interstitial deletion 13q comprises about 50% of the euchromatic regions of the long arm.

Cave:

The aberration was confirmed to be de novo therefore the genetic risk for the parents is less than 1%, this is caused by a possible gonadal mosaic in one of them (Fig. 4.49).

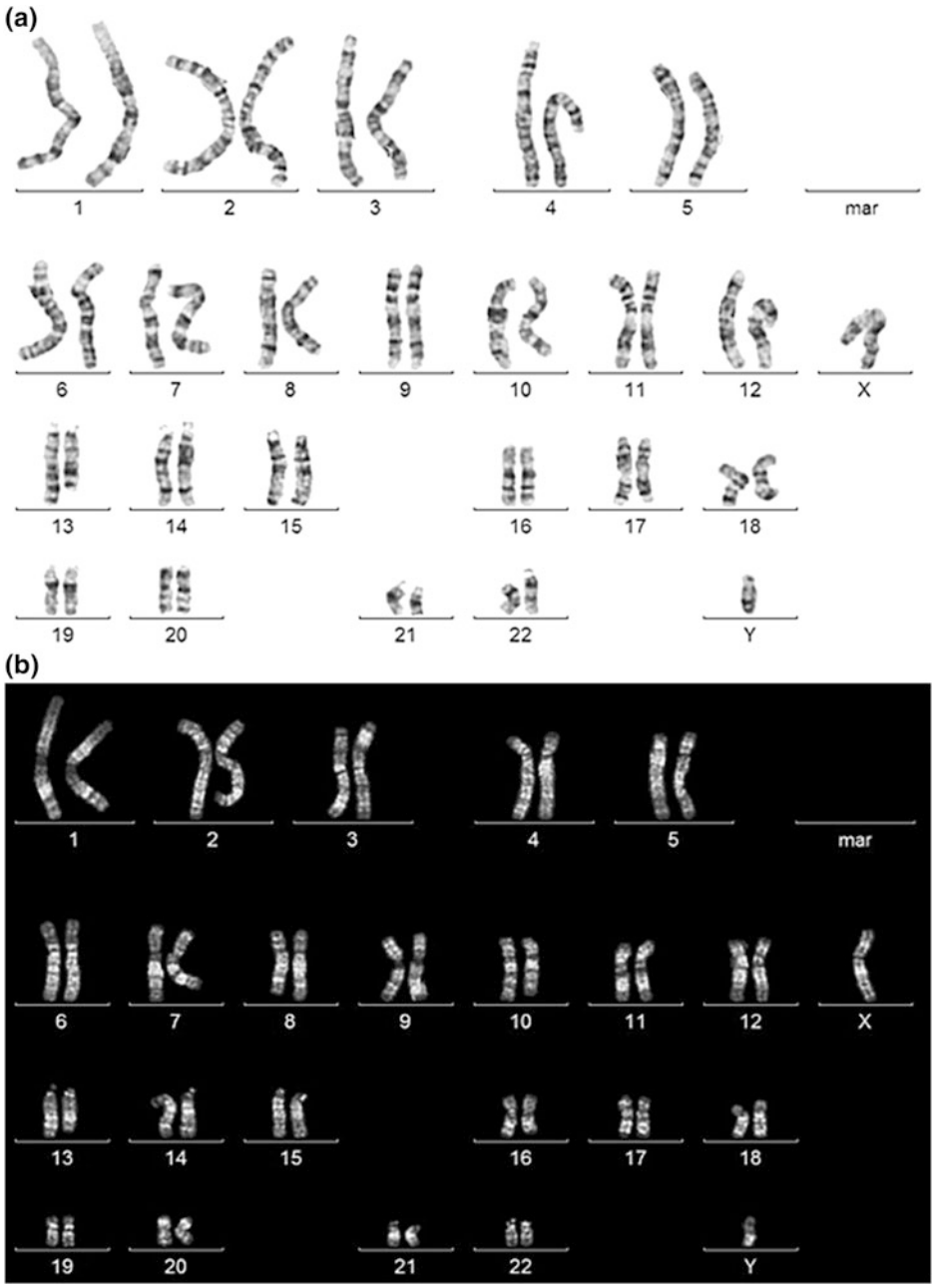

Fig. 4.49 Karyotype 46,XY,del(13)(q21.2q31). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 13, **e** ideograms of chromosome 13, interstitial deletion intermediate in the long arm

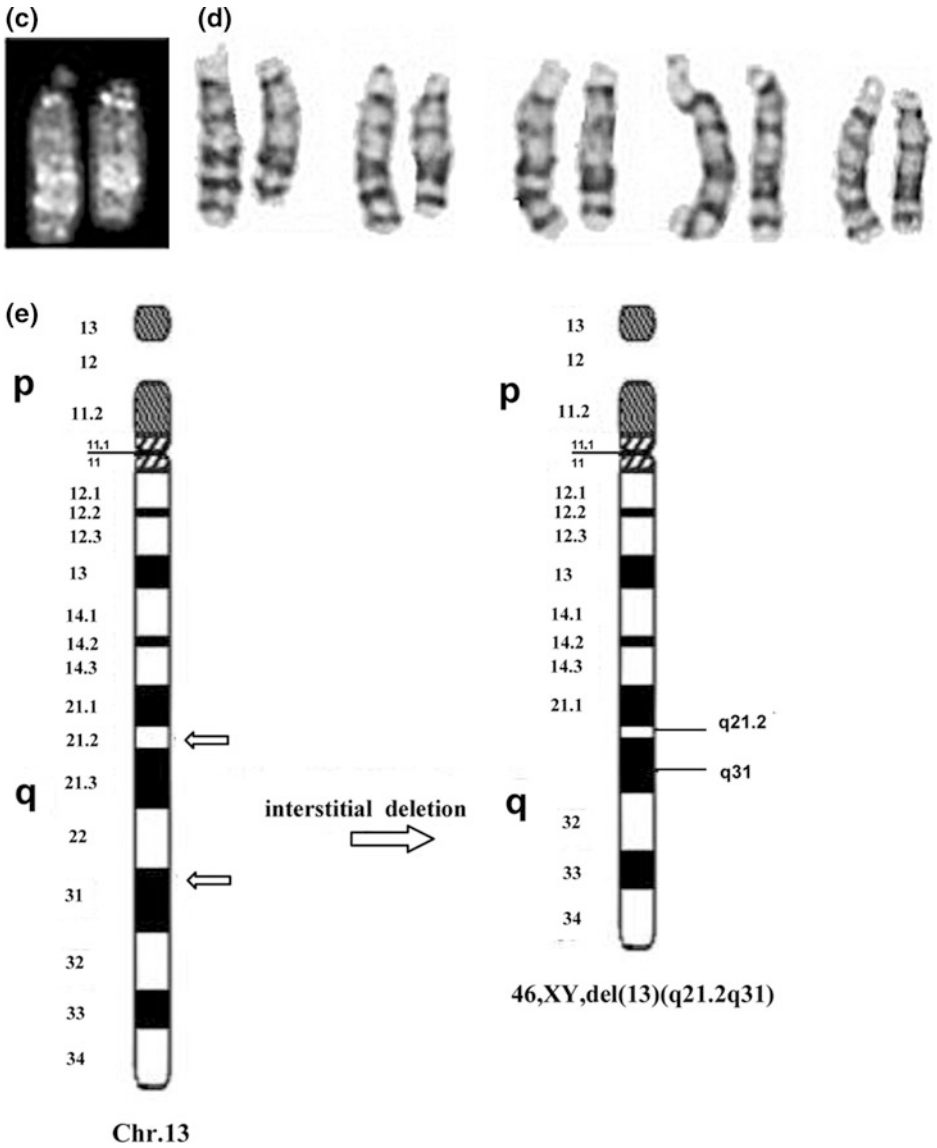

Fig. 4.49 (continued)

Case 10: Karyotype: 46,XY,del(15)(q11.2q13),inv(4)(p12q11.2)

Indication for chromosome analysis: Developmental retardation, dysmorphic features, phenotype of Prader Willi syndrome.

The proband has a euchromatic deletion 15, combined with a pericentromeric inversion of heterochromatic block in chromosome 4.

Morphology:

1. del(15)(q11.2q13)
   The proximal deletion in the long arm is the most frequent one in chromosome 13. The phenotype of the carrier is well defined.
2. inv(4)(p12q11.2)
   The inversion includes only the pericentromeric heterochromatin and is therefore without genetic relevance (see Case 2)

Cave:

Indications for chromosome investigations in the parents is given and should be combined with FISH applying LSI probes (Fig. 4.50).

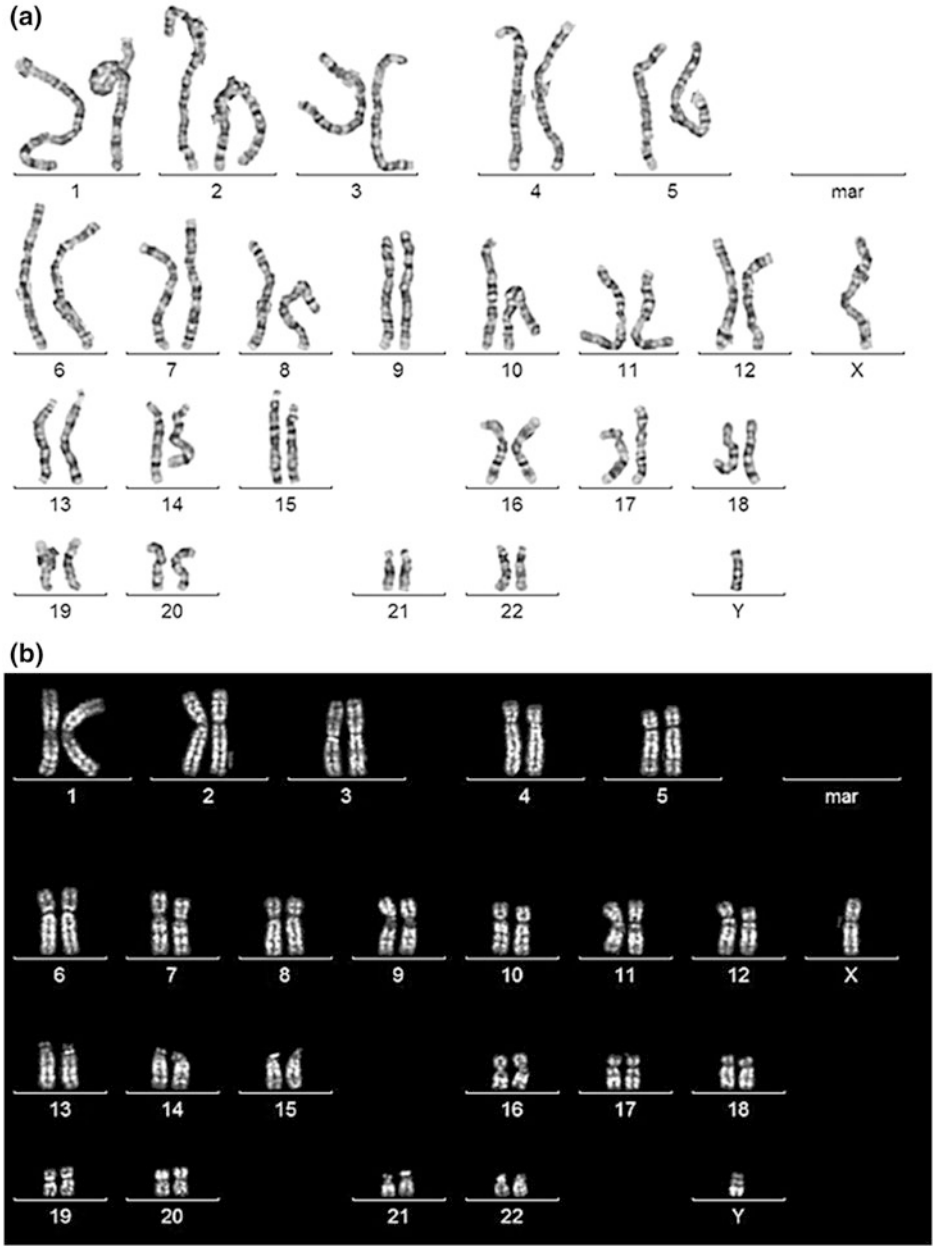

Fig. 4.50 Karyotype 46,XY,del(15)(q11.2q13),inv(4)(p12q11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 15, inv(4) see Case 2, **d** ideograms of chromosome 15, small proximal deletion

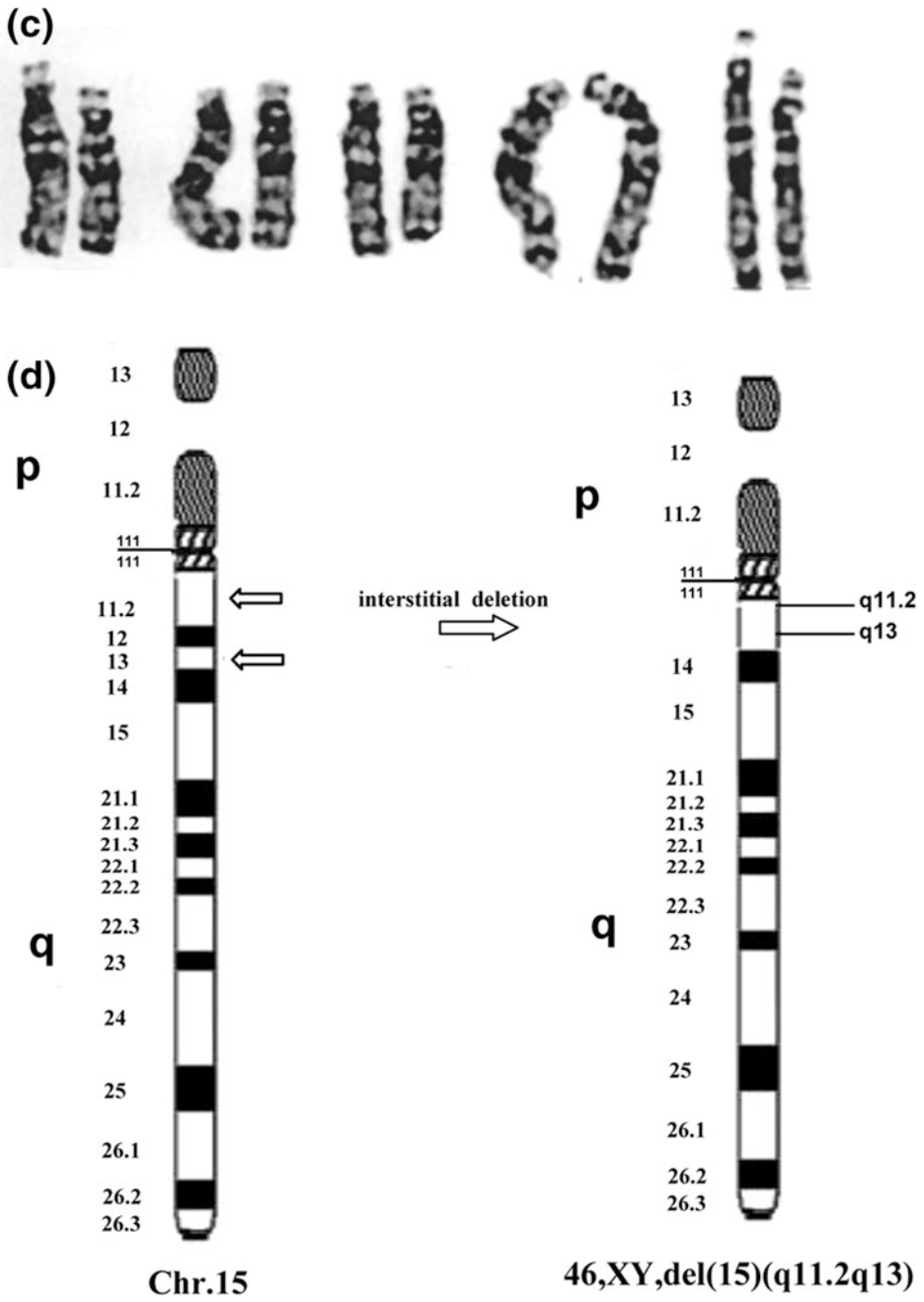

Fig. 4.50 (continued)

Case 11: Karyotype: 46,XY,del(17)(p11.2),inv(4)(p12q11.2)
Indication for chromosome analysis: Smith-Magenis syndrome.
Morphology:

The proximal, GC-rich band p11.2 in the short arm of chromosome 17 is deleted. Thus the following AT-band p12 has changed its position from the middle of the short arm to one neighboring the pericentromeric heterochromatin. The phenotype of the short arm changed from a tulip-shaped appearance to a U-shape.

Cave:

The de novo origin of the aberration has to be confirmed before genetic counseling (Fig. 4.51).

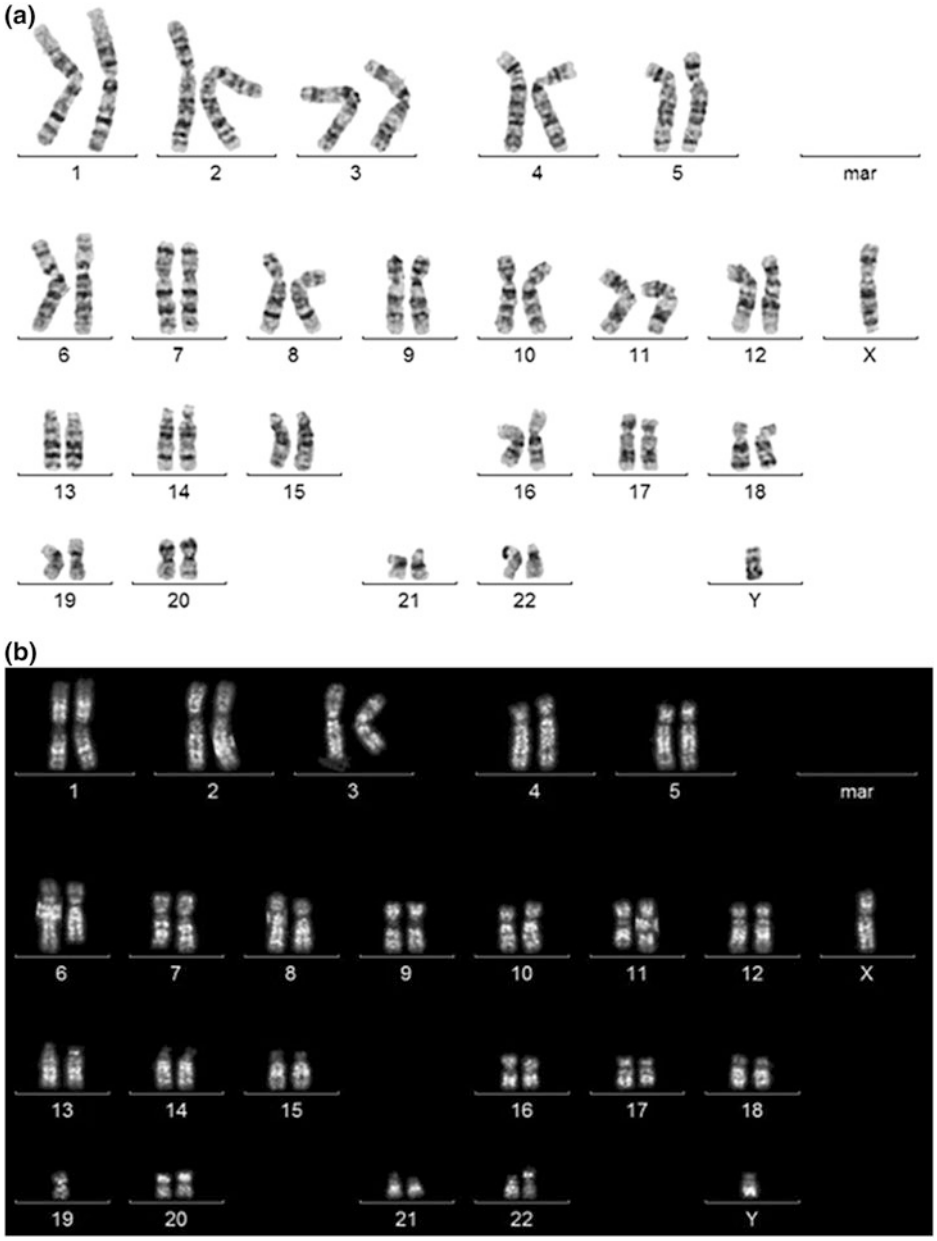

Fig. 4.51 Karyotype 46,XY,del(17)(p11.2)inv4(p12q11.2). **a** GTG-, **b** QFQ-banding, both 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 17, inv(4) see Case 2, **d** ideograms of chromosome 17, small interstitial short arm deletion, inv(4) see Case 2

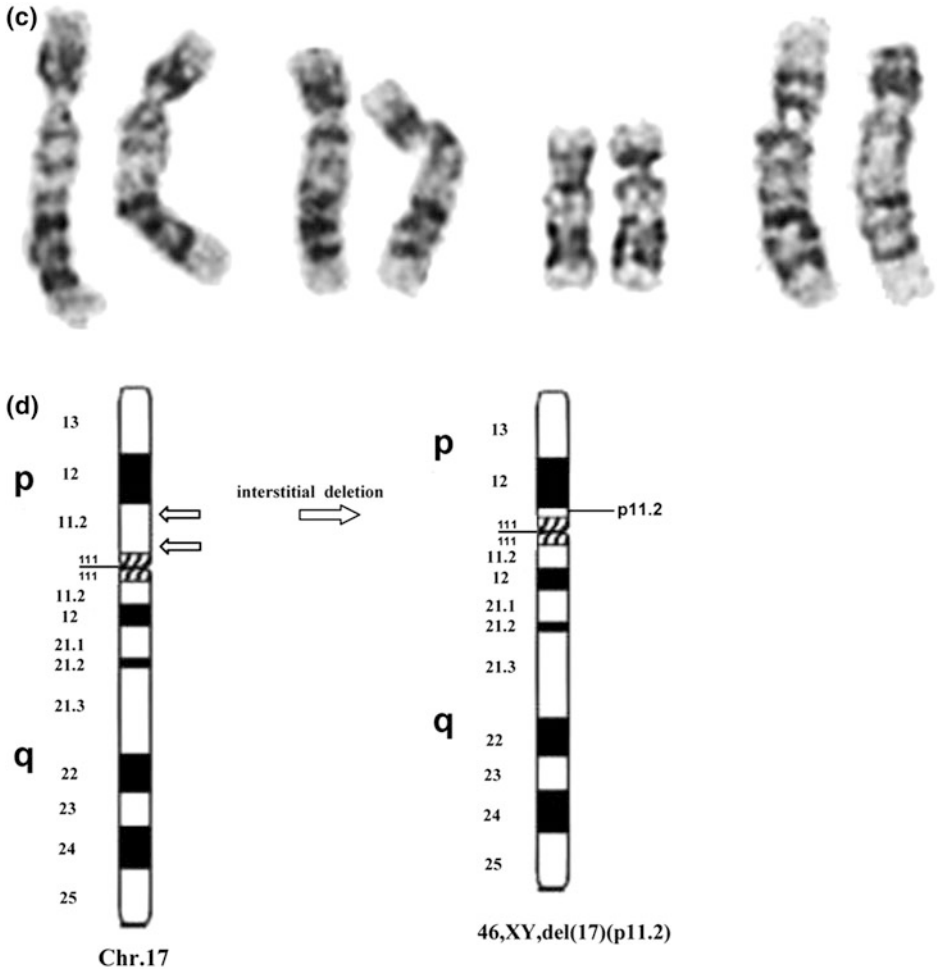

Fig. 4.51 (continued)

Case 12: Karyotype: 46,XX,del(17)(q23.1q23.3)

Chromosome analysis reveals two structural rearrangements, a euchromatic deletion and a heterochromatic inversion.

Indication for chromosome analysis: Unspecific developmental retardation.

Morphology:

The patient presents with an interstitial deletion of subband 17q23.2 in the distal region of the long arm. This and other comparable small structural aberrations are only detectable at a resolution of at least 700 bands per genome.

Cave:

Before genetic counseling an inversion should be excluded in the parents (Fig. 4.52).

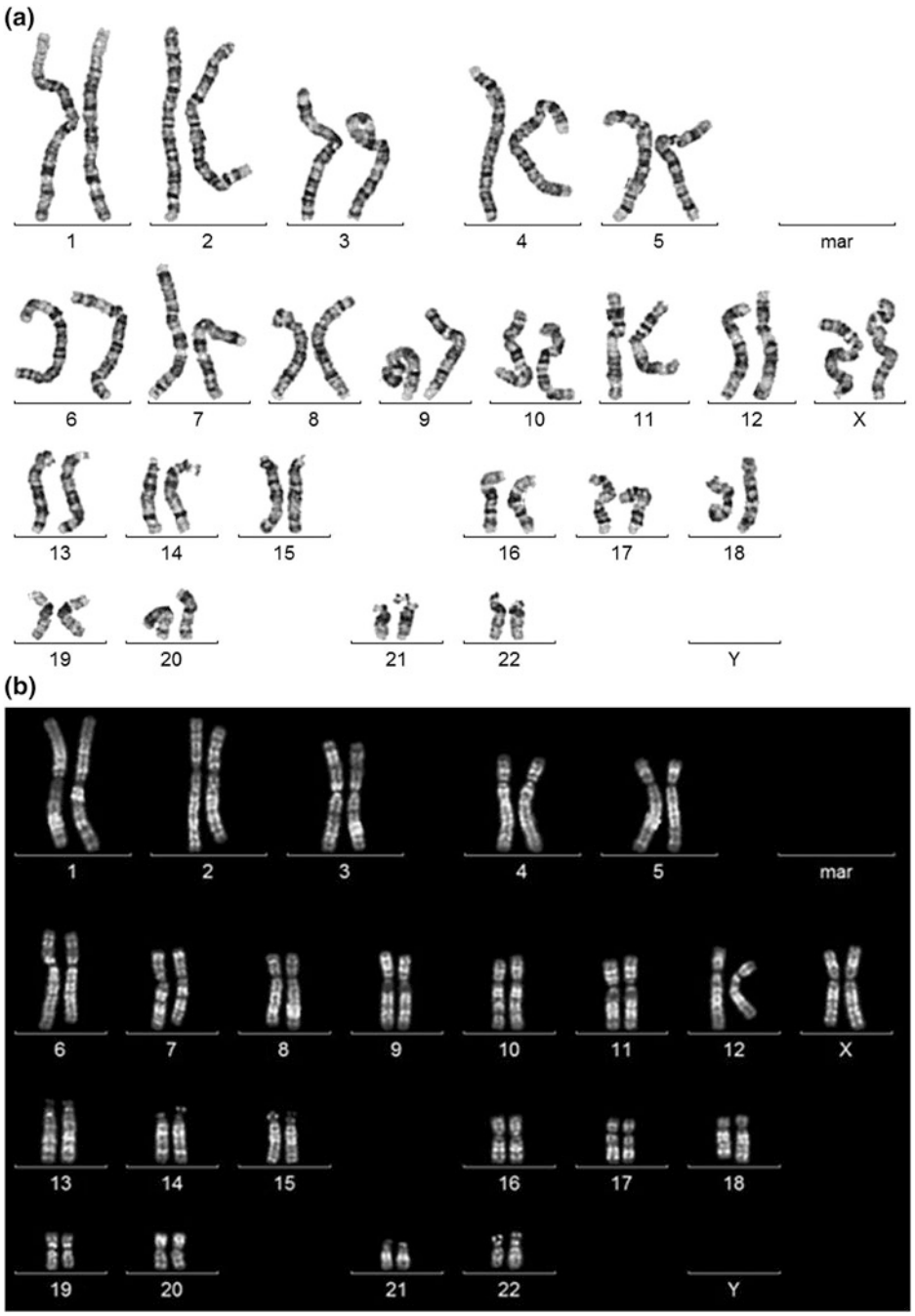

Fig. 4.52 Karyotype 46,XX,del(17)(q23.1q23.3). **a** GTG-, **b** QFQ-banding, 850 and 550 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 17, **d** ideograms of chromosome 17, interstitial long arm deletion

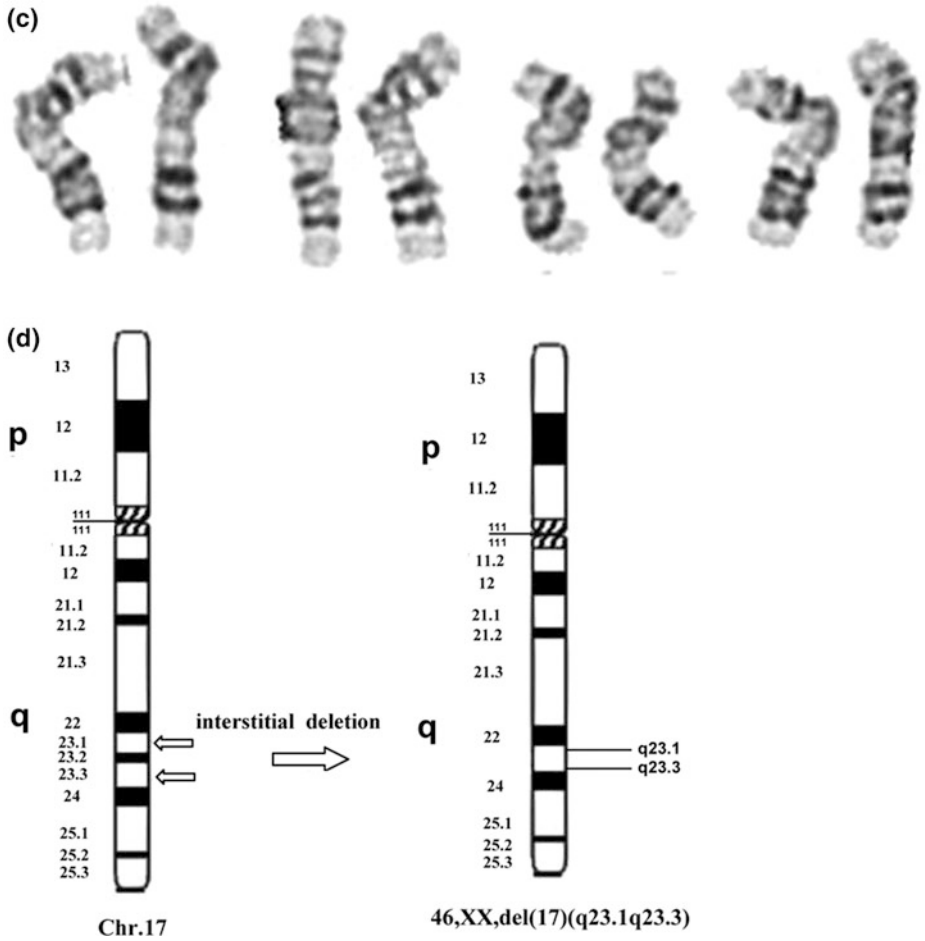

Fig. 4.52 (continued)

Case 13: Karyotype: 46,XX,del(18)(p11.2)dup(7)(q36)ish der(18),t(7;18)(q36;p11.2)(D18S552-,7QTEL20+),inv(9)(p12q13)

Indication for chromosome analysis: Developmental retardation phenotype of de Grouchy syndrome I.

The patient presents with one pericentric inversion 9 and a deletion derived from a parental translocation 7; 18.

Morphology:

1. del(18)(p11.2)
   The terminal deletion 18p is known as a frequent structural aberration and is called de Grouchy syndrome I. The phenotype of the patient is in good accordance with the clinical findings in the syndrome. The duplication 7q36 also present in the patient does not reveal any specific clinical symptoms. In the majority of cases known from the literature the deletion 18p originated de novo in the patients. But the case presented here demonstrates that other types of aberration such as inversions or translocations in the parents can lead to an unbalanced rearrangement in the child. In the case presented here, by microscopy only one of the translocation chromosomes (18) was detectable, the other one (7) was only analysable by subtelomere FISH.
2. inv(9)(p12q13)
   The pericentric inversion of chromosome 9 can be defined as polymorphism without genetic relevance. Both breakpoints are localised in the constitutive heterochromatin (see Case 40 of inversions).

Cave:

Only by additional FISH investigations the reciprocal translocation 7/18 could be analysed in the patient and the carrier mother. These findings are an impressive example for the relevance of additional investigations in structural chromosome aberrations (Fig. 4.53).

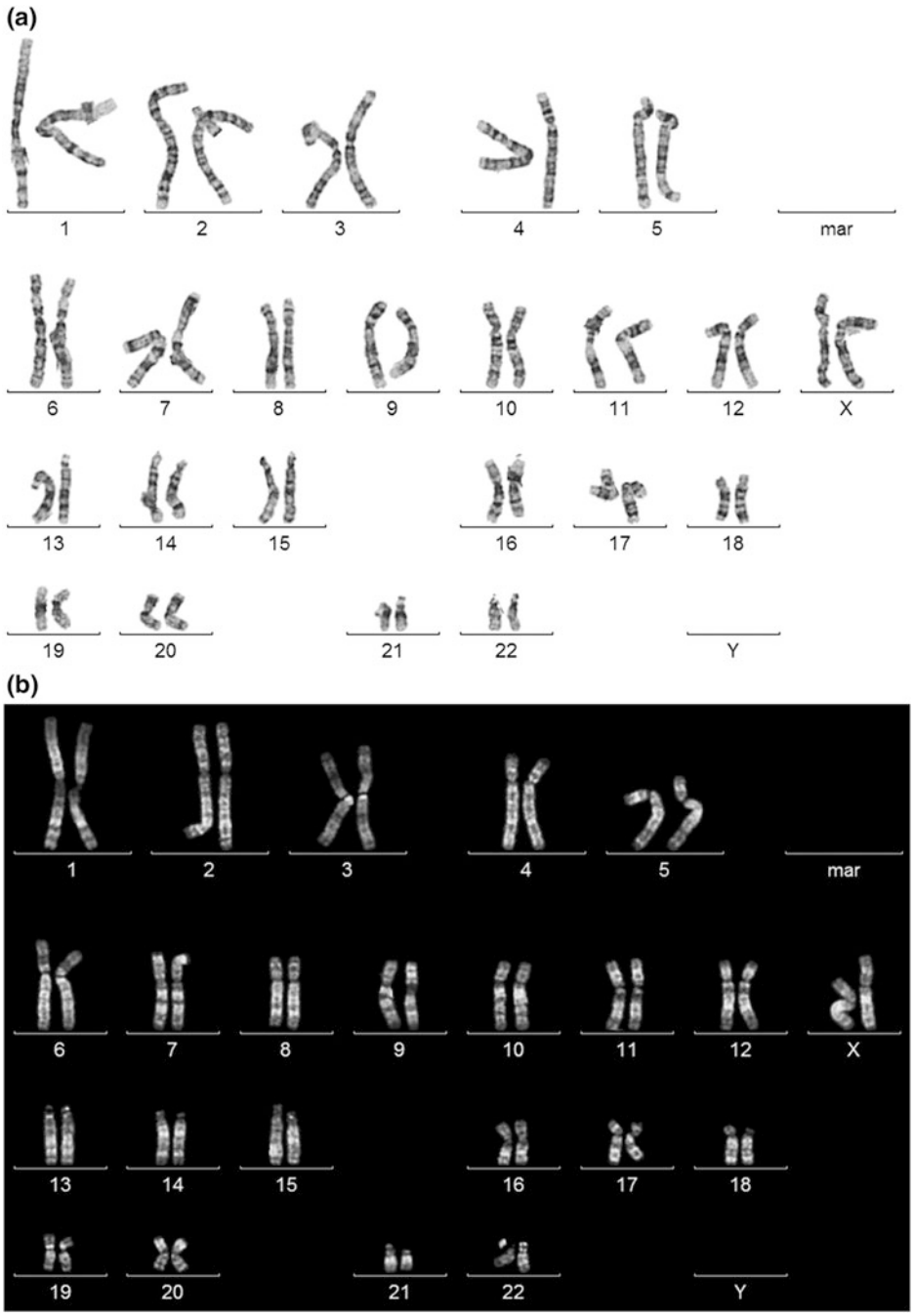

Fig. 4.53 Karyotype 46,XX,del(18)(p11.2)dup(7)(q36),t(7;18)(q36;p11.2),inv(9)(p12q13). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 18, inv(9) see Case 40 of inversions, **d** ideograms of breakpoints and rearrangements of unbalanced reciprocal translocation 7;18

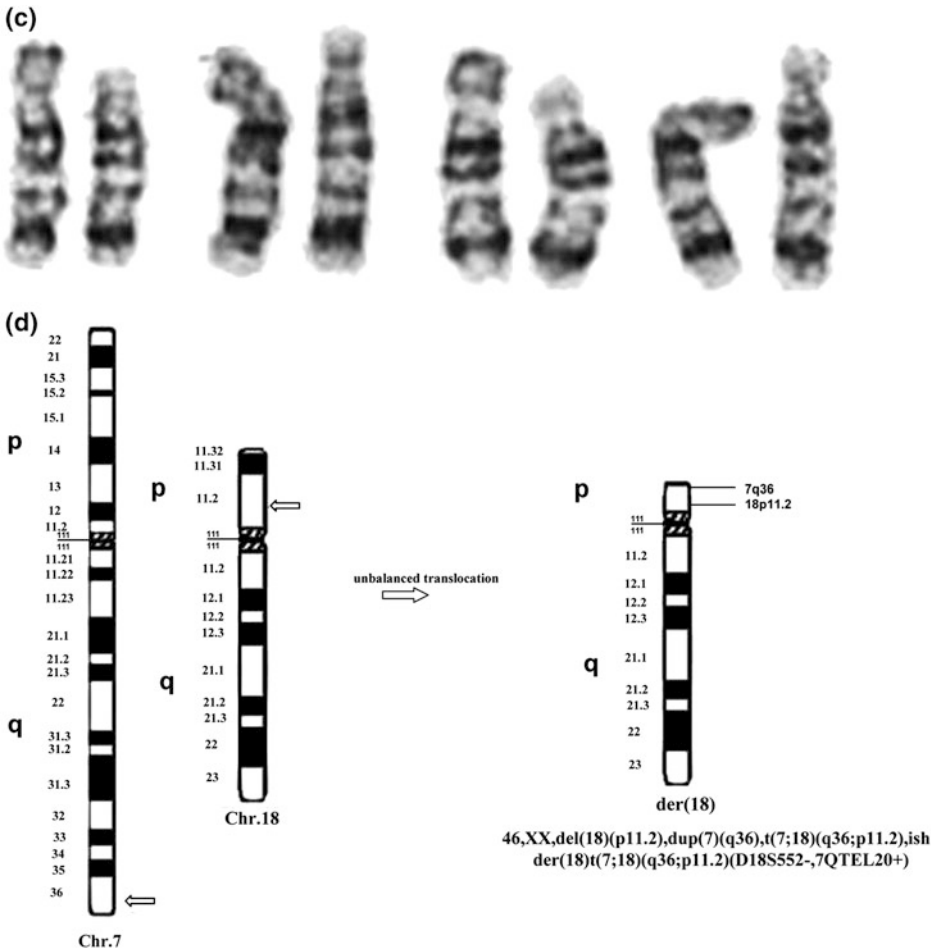

Fig. 4.53 (continued)

Case 14: Karyotype: 46,XX,del(18)(q21.3),inv(4)(p12q11.2)

Indication for chromosome analysis: Mild developmental retardation, morphological peculiarities according to de Grouchy syndrome II.

Morphology:

1. del(18)(q21.3)
   The terminal de novo deletion in the long arm of chromosome 18 encloses about 25% of the total length of the chromosome. The centromere index has changed to an almost metacentric position and the characteristic AT-band q22 is deleted. The breakpoint q21.3 is a frequent region of rearrangements.
2. inv(4)(p12q11.2)
   (see Case 2)

Cave:

The de novo origin of the deletion has always to be confirmed before genetic counseling of the family (Fig. 4.54).

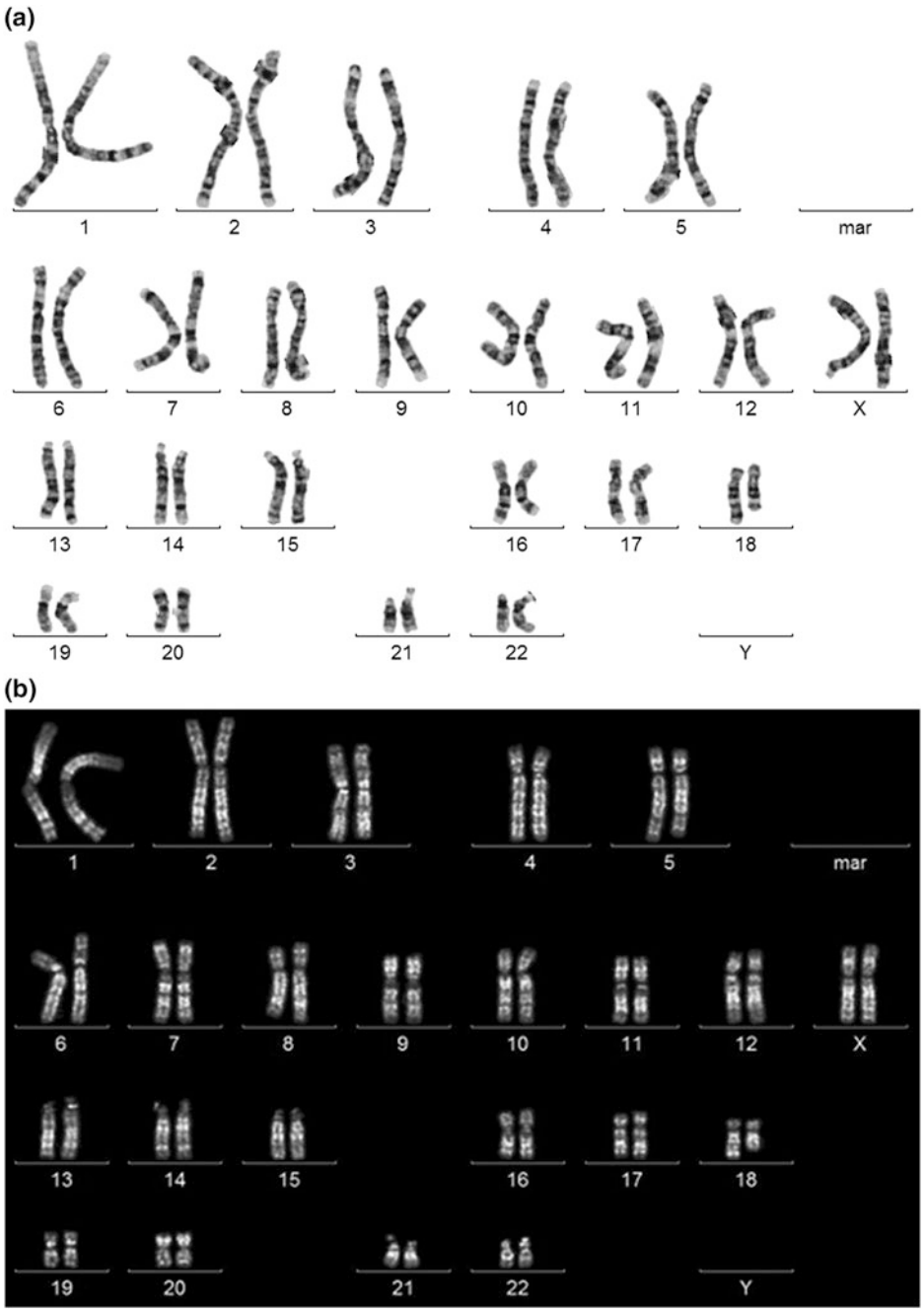

Fig. 4.54 Karyotype 46,XX,del(18)(q21.3),inv(4)(p12q11.2). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted chromosome 18, inv(4) see Case 2 of deletion, **d** ideograms of chromosome 18, terminal deletion in the long arm, inv(4) see Case 2 of deletions

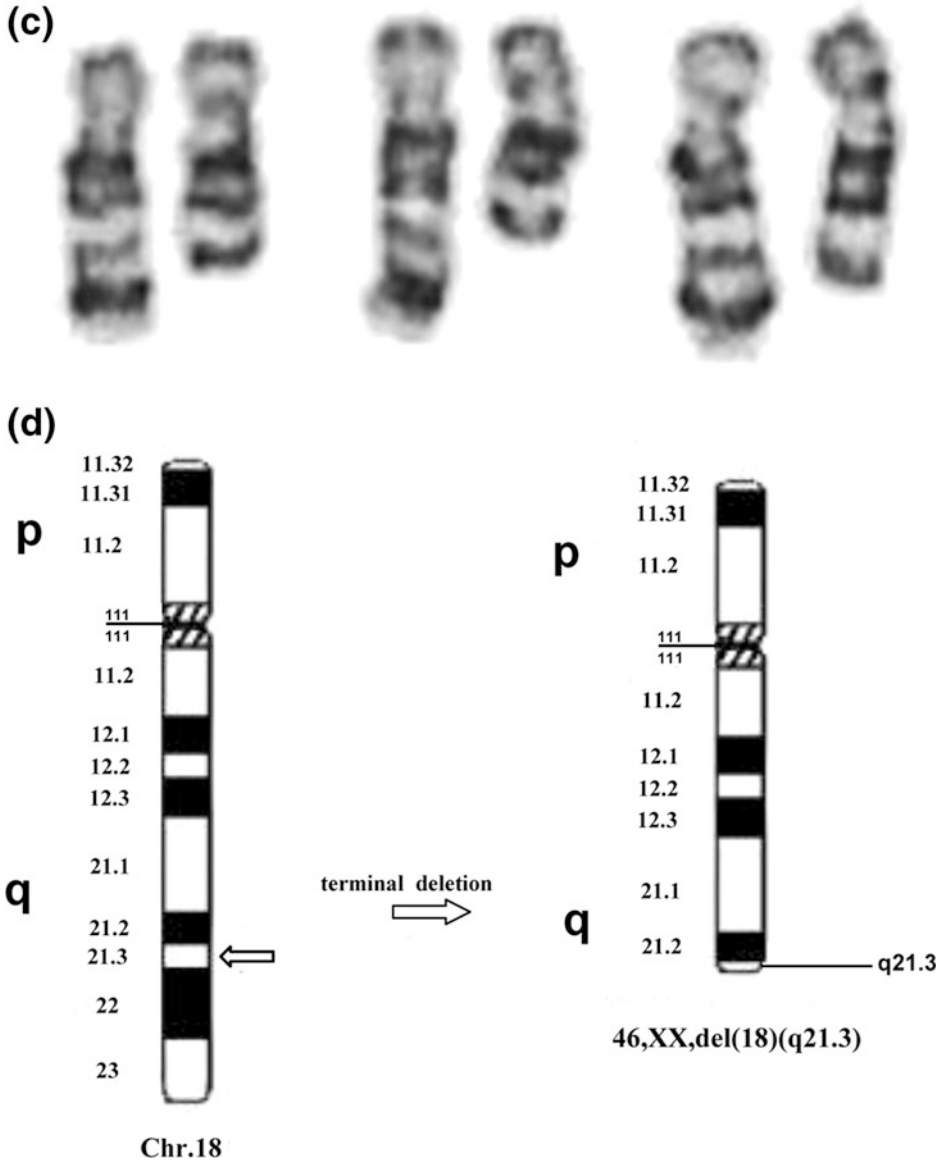

Fig. 4.54 (continued)

Case 15: Karyotype: 46,X,del(X)(p11.23)
Indication for chromosome analysis: Clinical symptoms of Turner syndrome.
Morphology:

The terminal deletion of the short arm of the X-chromosome comprises about 85% of its total length. The deleted chromosome is stable in its inheritance in the course of cell divisions. A second cell line was not detectable.

Cave:

The chromosomes of the mother should be investigated before genetic counseling to exclude a balanced translocation (Fig. 4.55).

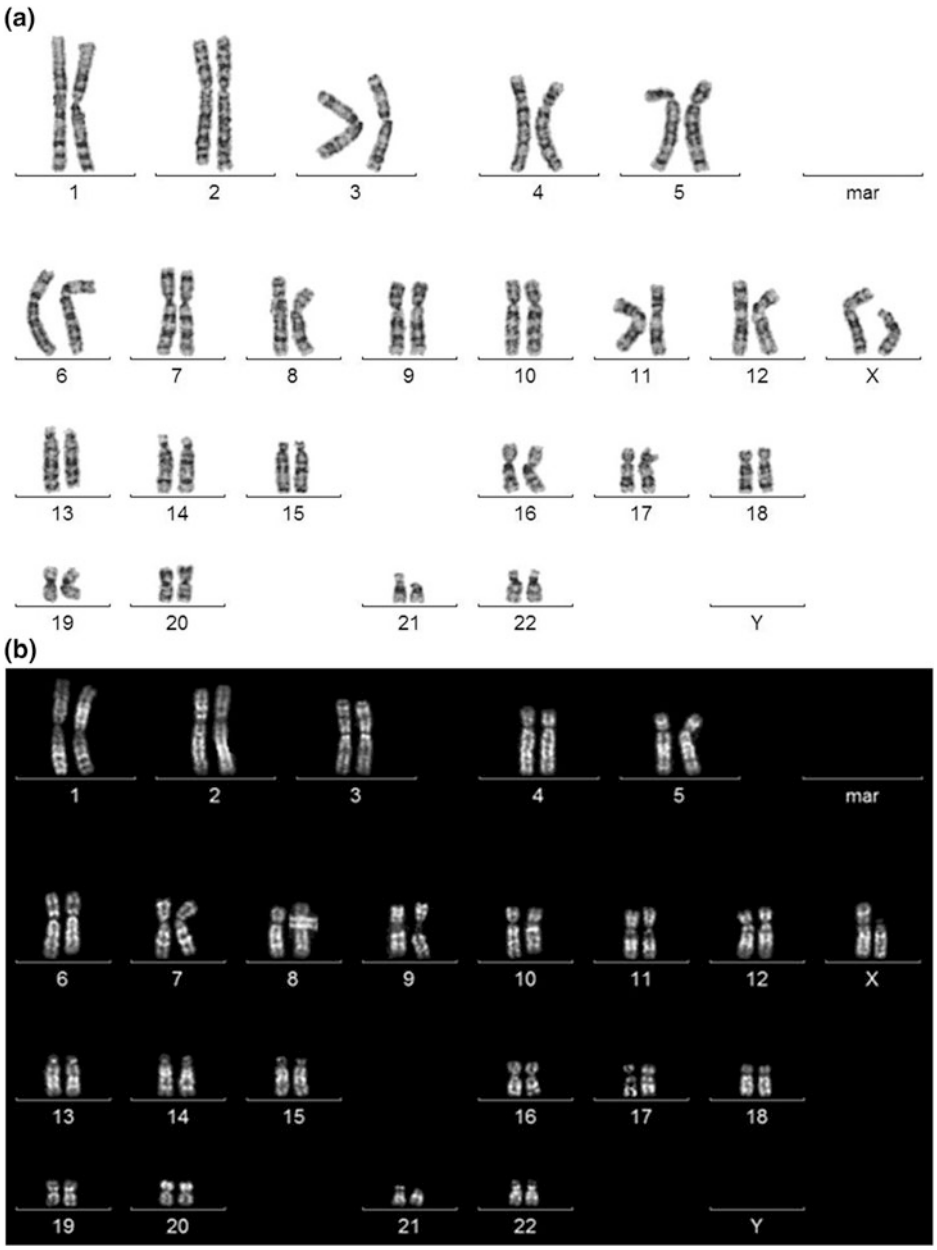

Fig. 4.55 Karyotype 46,X,del(X)(p11.23). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted X-chromosome, **d** ideograms of the X-chromosome, large distal deletion in the short arm

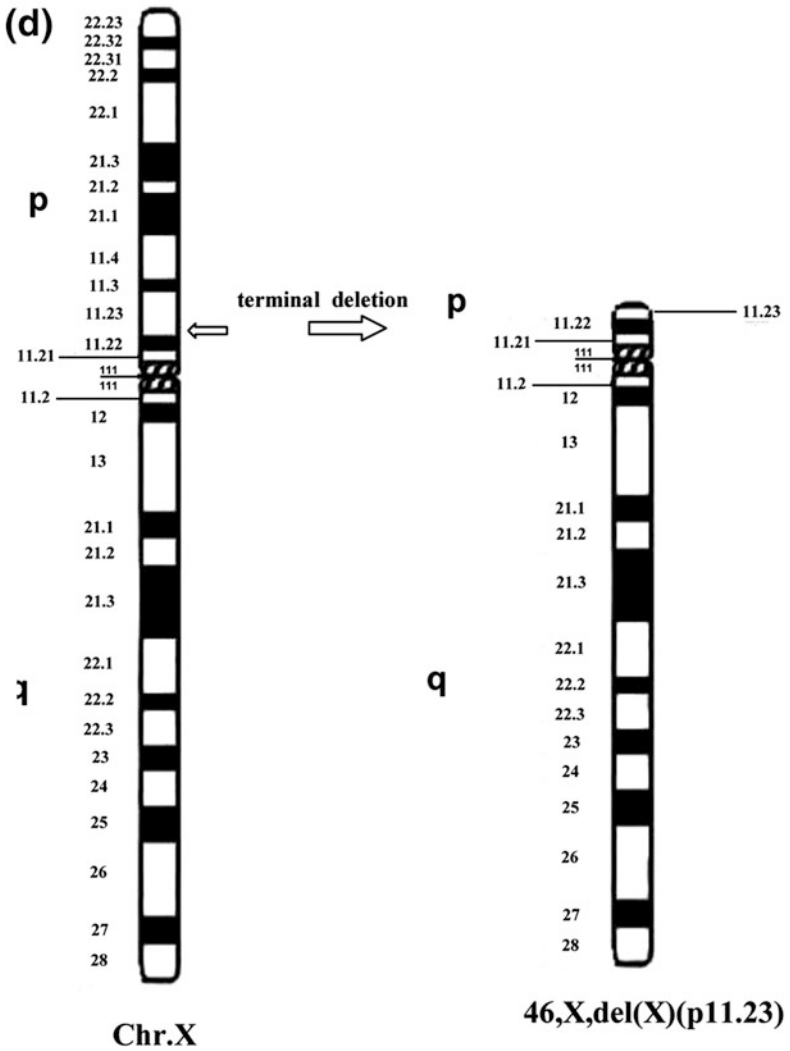

Fig. 4.55 (continued)

Case 16: Karyotype: 46,X,del(X)(p22.1)
Indication for chromosome analysis: Sterility.

Morphology:

The deleted X-chromosome has the breakpoint in p22.1 a well-known frequent locus of aberration induction. About 30% of the distal short arm got lost, the characteristic bands p21.1 to p21.3 have been preserved.

Cave:

No further chromosome investigations before genetic counseling are indicated (Fig. 4.56).

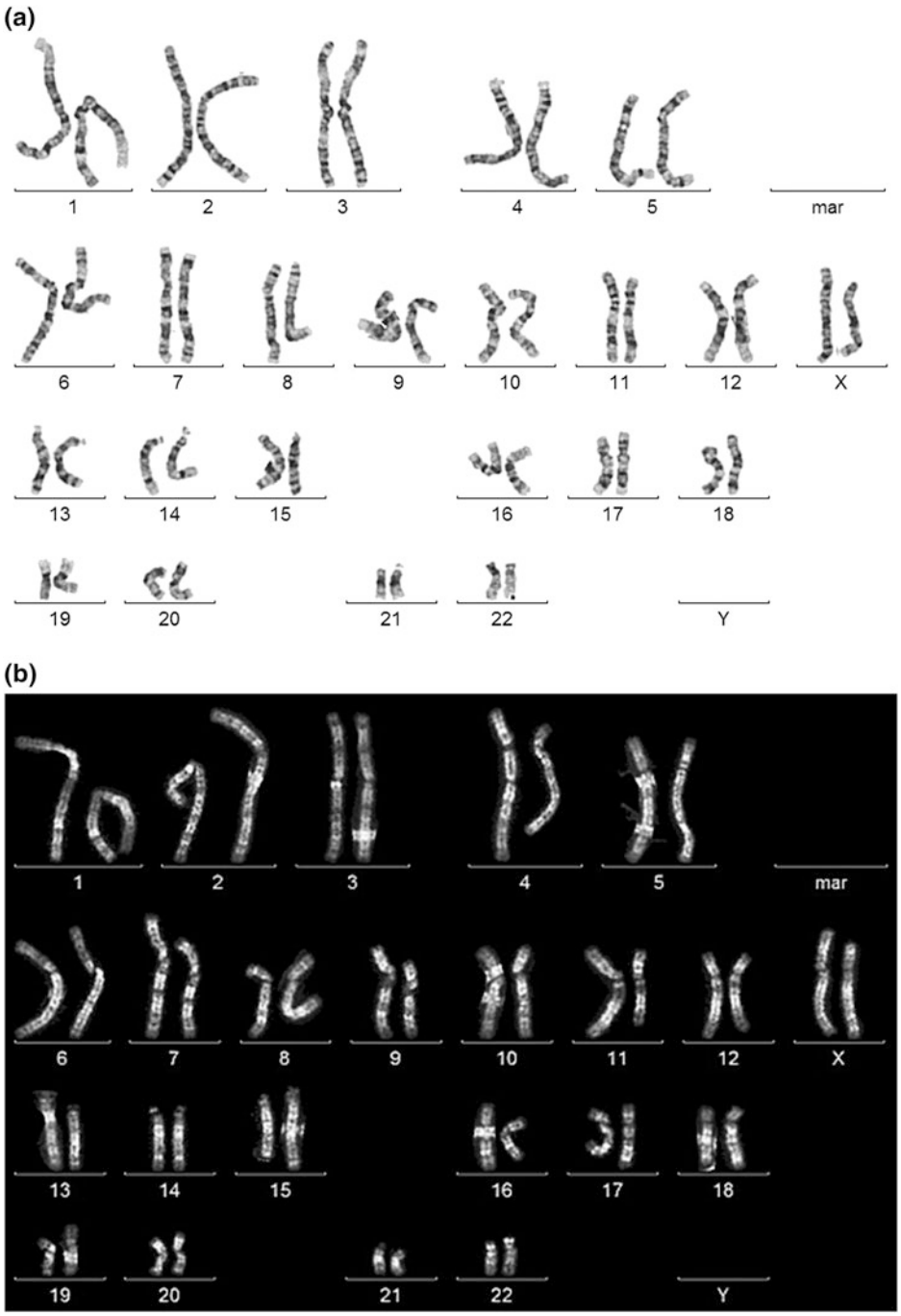

Fig. 4.56 Karyotype 46,X,del(X)(p22.1). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted X-chromosome, **e** ideograms of the X-chromosome, terminal short arm deletion

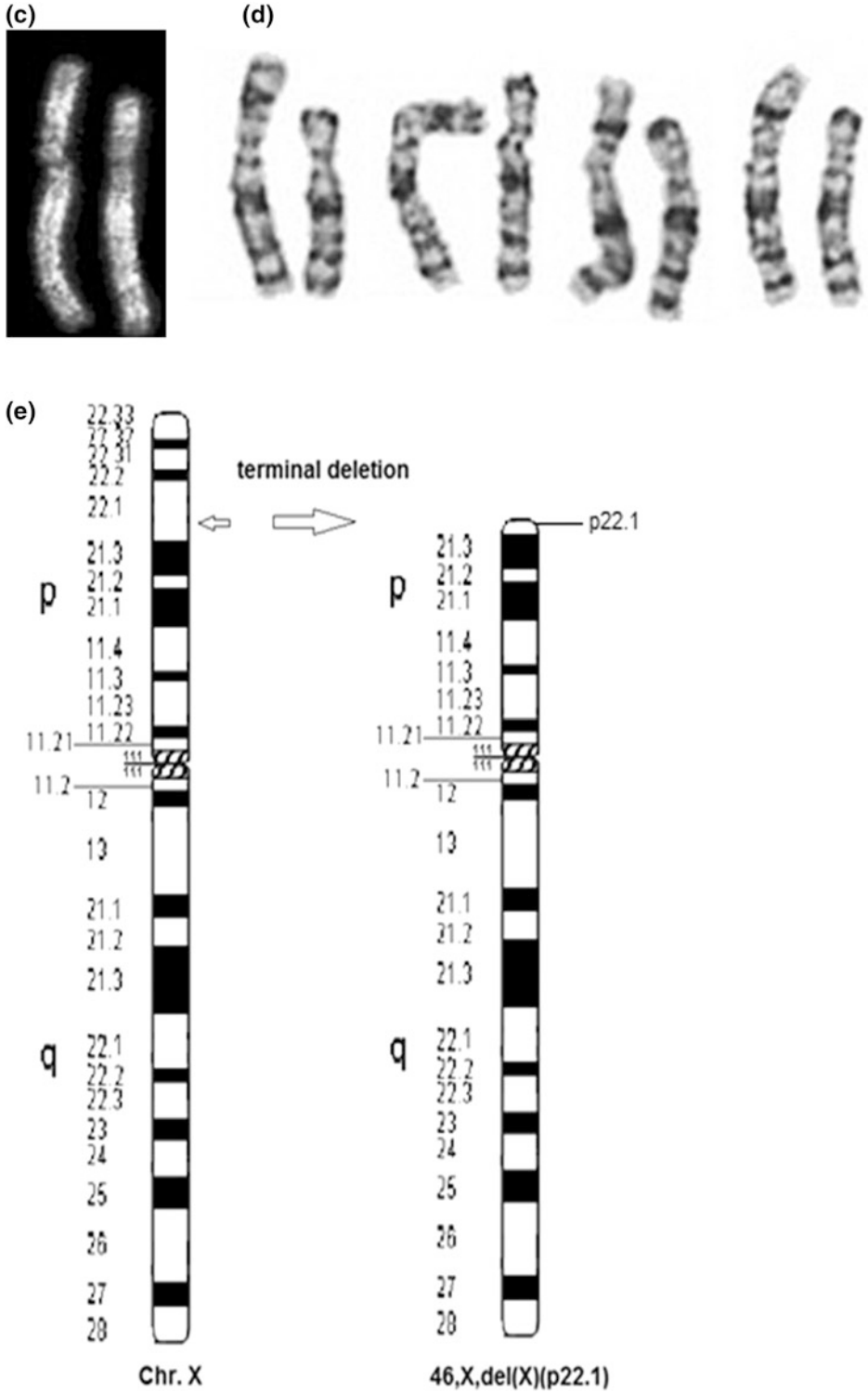

Fig. 4.56 (continued)

Case 17: Karyotype: 46,X,del(X)(p22.11p22.2),inv(4)(p12q11.2)
Indication for chromosome analysis: Increased number of abortions, normal phenotype, uterus bicornis.

Morphology:

1. del(X)(p22.11p22.2)
   Interstitial deletion in the distal region of the short arm of the X-chromosome. About 20% of its total length got lost. The deleted segment is not easy to localise, therefore a resolution of at least 550 bands is required.

2. inv(4)(p12q11.2)
   (see Case 2)

Cave:

The deleted region in Xp comprises 17 relevant genes. As the phenotype of the patient is normal a screwed inactivation of the deleted chromosome can be expected. Therefore genetic counseling has to take into account that 50% of male offspring will be carrier of a 13.2 Mb deletion which can be expected to be lethal. 50% of the female offspring will be carrier of the deletion as their mother, but if not a screwed inactivation of the aberrant chromosome takes place in the same way, it can present with a pathologic phenotype (Fig. 4.57).

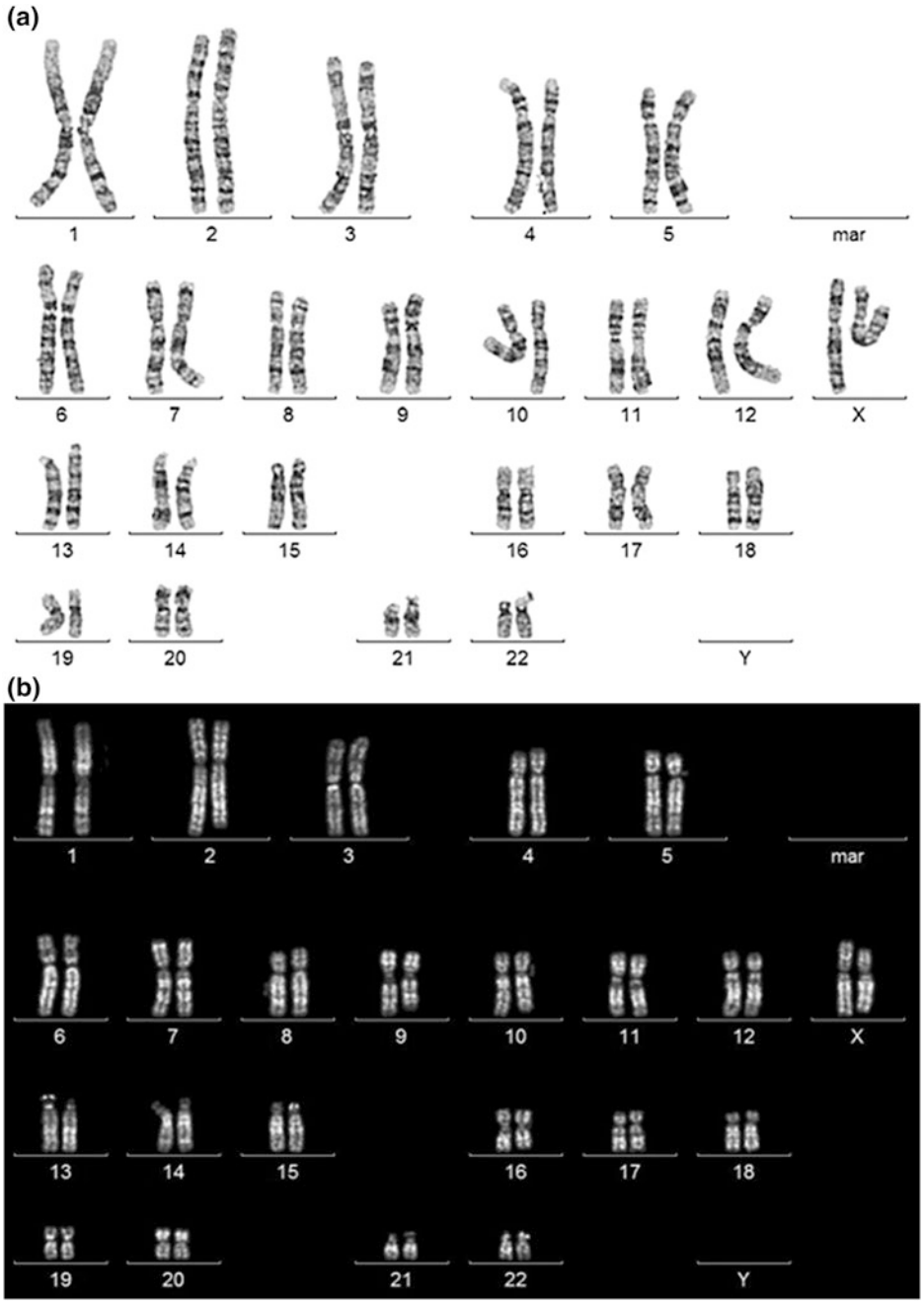

Fig. 4.57 Karyotype 46,X,del(X)(p22.1p22.2),inv(4)(p12q11.2). **a** GTG-, **b** QFQ-banding, 600 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted X-chromosome, inv(4) see Case 2, **e** ideograms from the X-chromosome, small interstitial deletion in the short arm, inv(4) see Case 2 of deletions

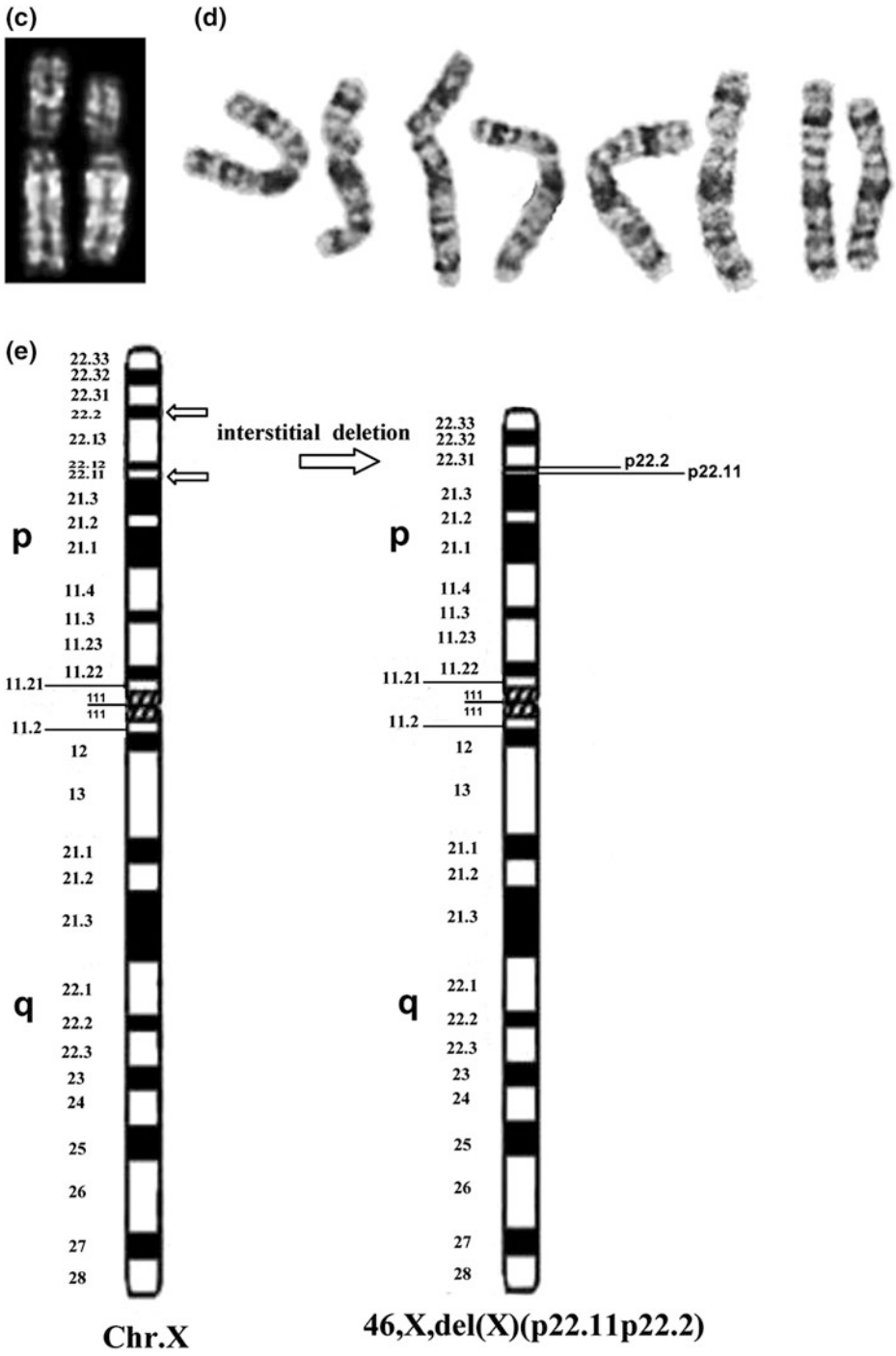

Fig. 4.57 (continued)

Case 18: Karyotype: 46,X,del(X)(q21.2)
Indication for chromosome analysis: Infertility.

Morphology:

The aberrant X-chromosome shows a terminal deletion in the long arm which comprises about 50% of its total length. The deletion is even detectable at a lower banding resolution but for exact definition of the breakpoint at least 550 bands per genome are required.

Cave:

Genetic counseling should be offered to discuss the possibilities of infertility treatment, including after additional investigations the possible occurrence of screwed X-inactivation (Fig. 4.58).

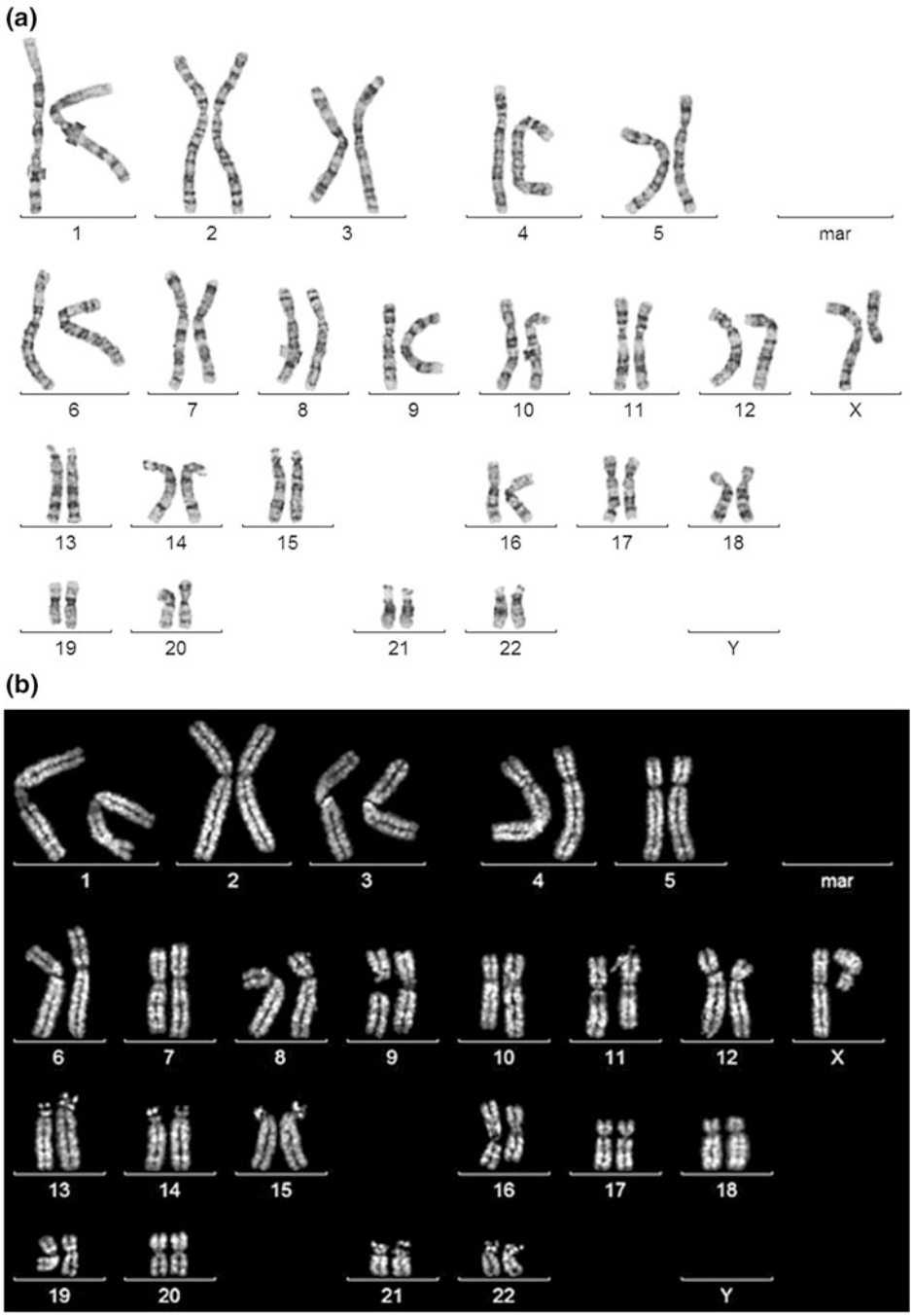

Fig. 4.58 Karyotype 46,X,del(X)(q21.2). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** QFQ-, **d** GTG-banding chromosomes from different mitoses, *left* normal, *right* deleted X-chromosome, **e** ideograms of the X-chromosome, large distal deletion in the long arm

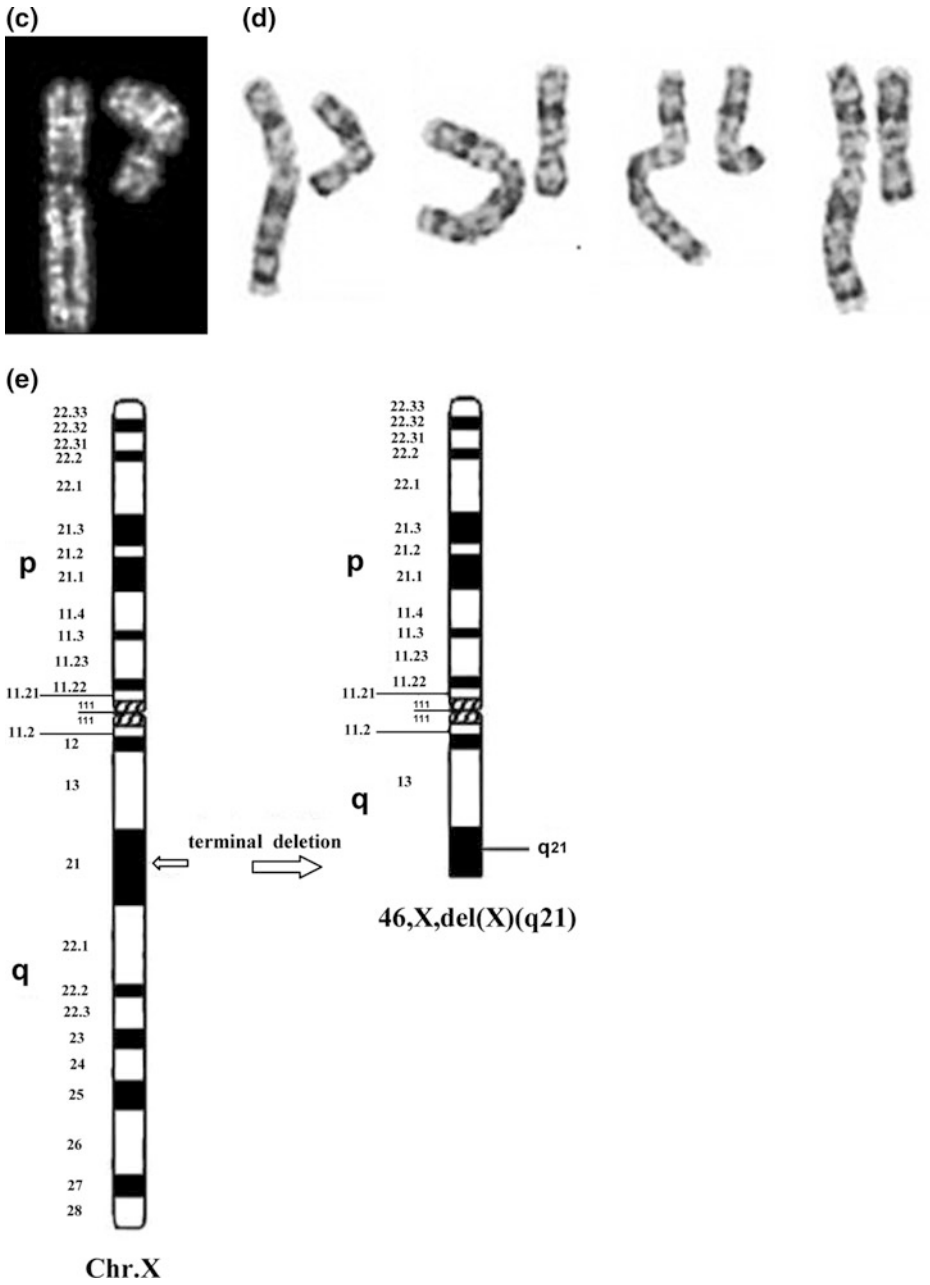

Fig. 4.58 (continued)

Case 19: Karyotype: 46,X,del(X)(q27.2)
Indication for chromosome analysis: Infertility.

Morphology:

The terminal part of the long arm of the X-chromosome is deleted. It comprises about 10% of the total length of the long arm. In this case a resolution of about 850 bands per genome was necessary, to define the breakpoint in the subband q27.2.

Cave:

If pregnancy can be induced the patient should be informed about possible risk factors in male offspring (Fig. 4.59).

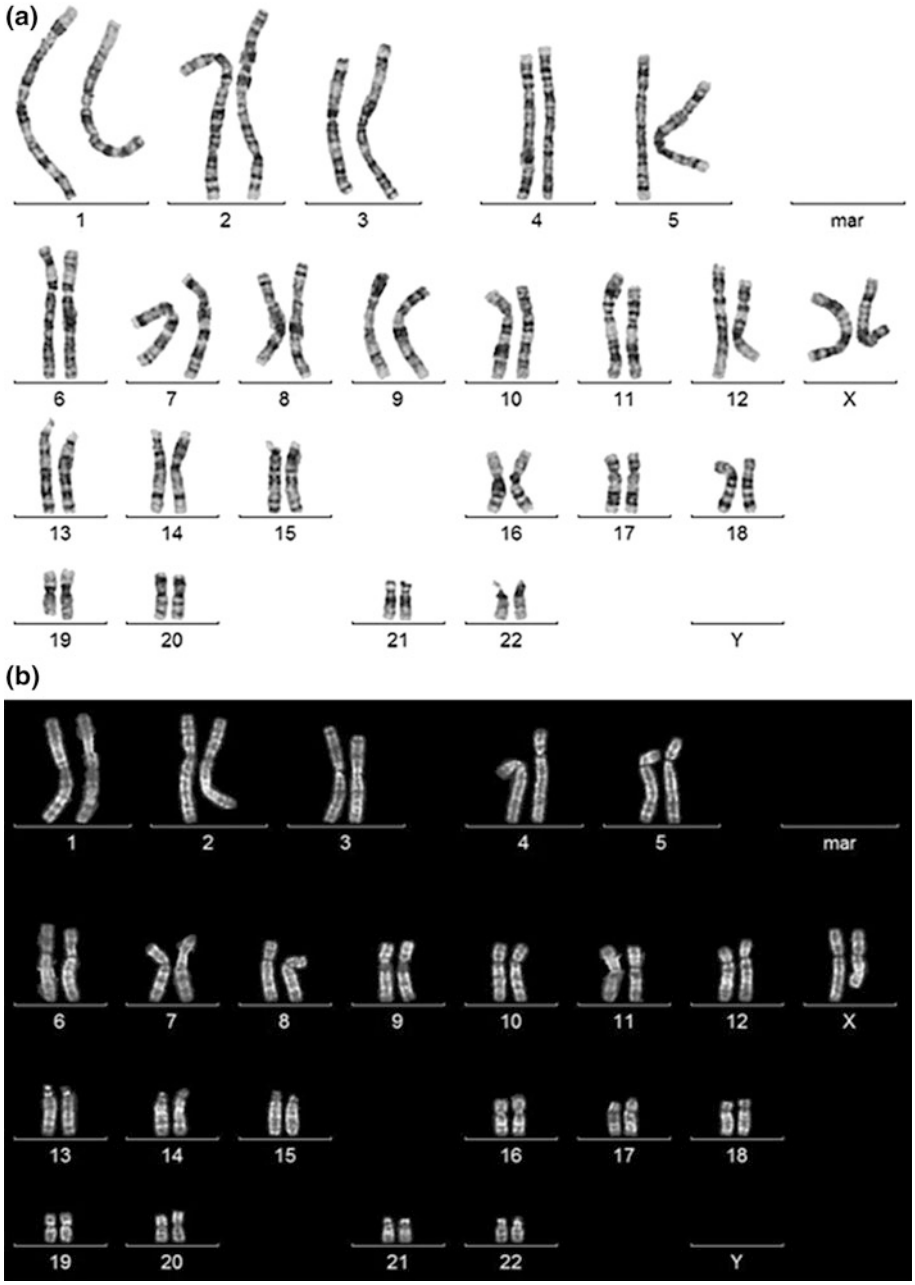

Fig. 4.59 Karyotype 46,X,del(X)(q27.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* deleted X-chromosome, **e** ideograms of the X-chromosome, small terminal long arm deletion

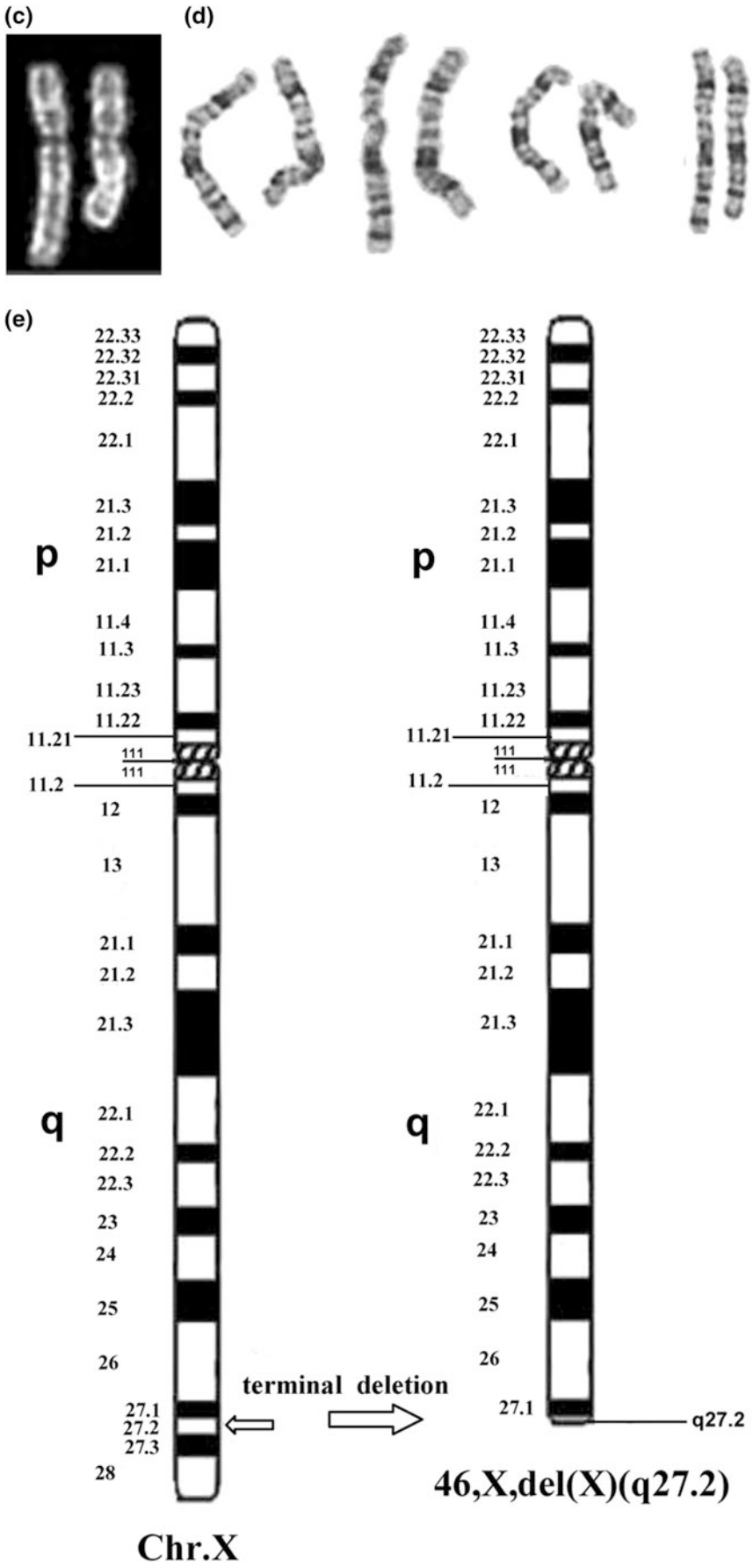

Fig. 4.59 (continued)

Case 20: Karyotype: 46,X,del(Y)(q11.22)

Indication for chromosome analysis: Azoospermia.

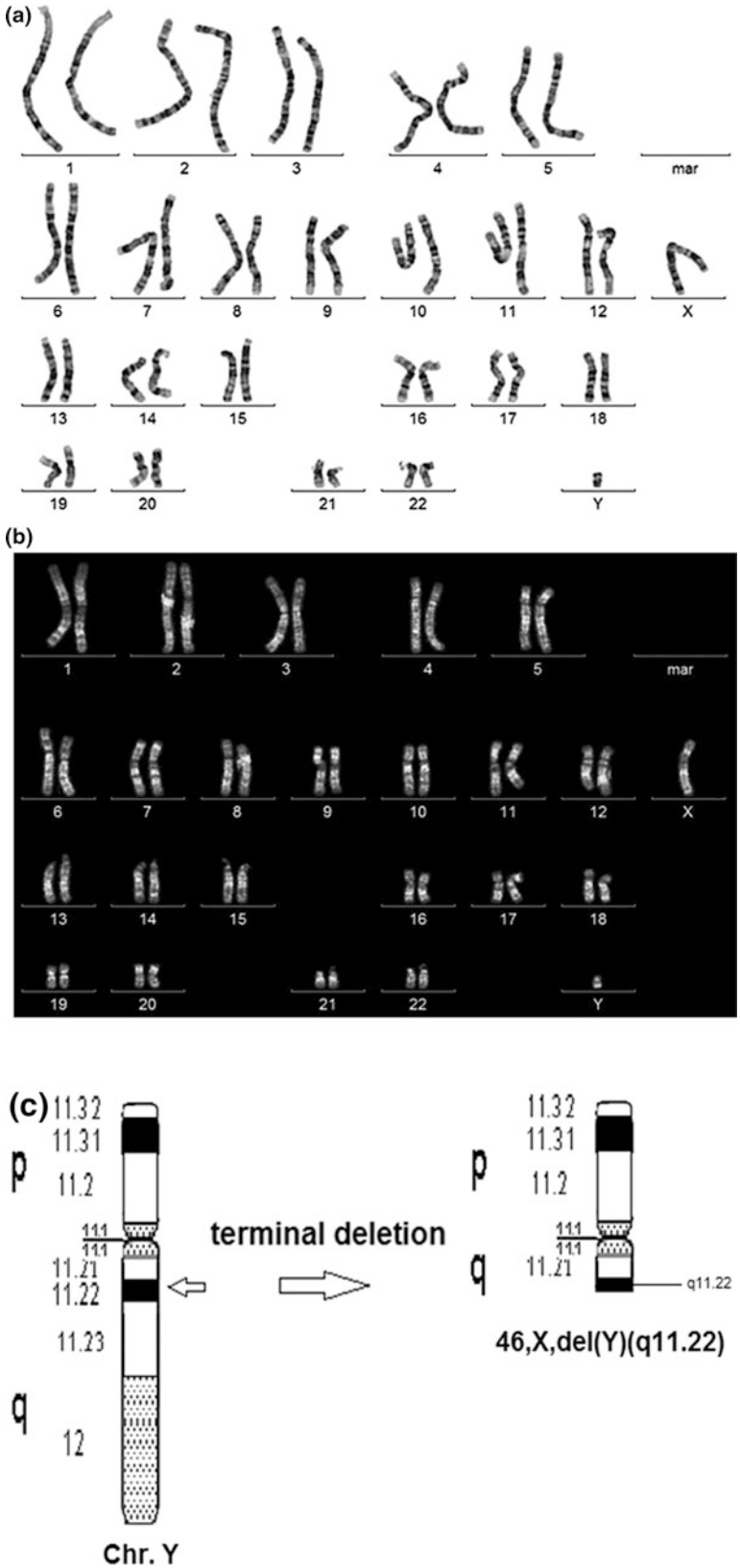

Fig. 4.60 Karyotype 46,X,del(Y)(q11.22). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c** ideograms of the Y-chromosome, deletion in the distal long arm

Morphology:

The aberrant Y-chromosome shows a terminal deletion of the complete heterochromatic block in q12 and of the adjacent euchromatin with breakpoint in q11.22.

Cave:

The relevance of the deletion of the AZF-region has to be explained to the patient (Fig. 4.60).

Summary

Out of the own investigation group 20 case reports were presented in detail. The interchromosomal distribution of the aberrant chromosomes is relatively equal as to the autosomes, though the small chromosomes 19–22 were not involved. The gonosomes X and Y were overrepresented compared to the autosomes, which is caused by the main investigation group of sterility patients (70:30%).

It was an unexpected observation that in 2 cases (N° 6 and 13) the aberration was not an isolated deletion, but the karyotype revealed a second structural abnormality. Therefore these cases belong to the group of complex chromosome rearrangements (CCR), and this group requires according to recent findings additional molecular genetic investigations.

One case (N° 7) shows beside mitoses with a deletion of chromosome 8 one metaphase with a normal karyotype. This leads to the conclusion that the deletion originated in the postzygotic phase, and this has to be regarded as a very rare process. In a further case (N°13) additional molecular genetic investigations showed, that the patient has not only a deletion: his chromosome abnormality is the unbalanced form of a reciprocal translocation 7/18 of parental origin. This case makes it clear how relevant are the extended investigations even in simple appearing cases of structural changes of the chromosome.

If the localisation of the breakpoints in the chromosomes of the investigation group is analysed, 15 of the deletions were terminal and 5 interstitial aberrations. Even if the deletions are separated into autosomal and gonosomal abnormalities this distribution is the same even taking into account the small number of cases.

The relevance of parental analyses before genetic counseling could be demonstrated.

4.2.1.3 Duplications

1 46,XX,dup(9)(p11.2)
2 46,XY,dic(9)(pter→q11::p12→qter)
3 ♀ 46,X,dup(X)(p11.4p21.2)y
♂ 46,dup(X)(p11.4p21.2)y

Case 1: Karyotype: 46,XX,dup(9)(p11.2)

Indication for chromosome analysis: Increased rate of abortions.

Morphology:

The additional band in p11.2 is dark staining (AT-rich) after GTG banding and negative after CBG staining. In the aberrant chromosome 9 the arm index has changed the chromosome into a more metacentric structure. The FISH analysis defined the additional band as a euchromatic variant without genetic relevance.

Cave:

In the pathologic course of a future pregnancy the karyotype of the conceptus should be analysed to exclude meiotic abnormalities (Fig. 4.61).

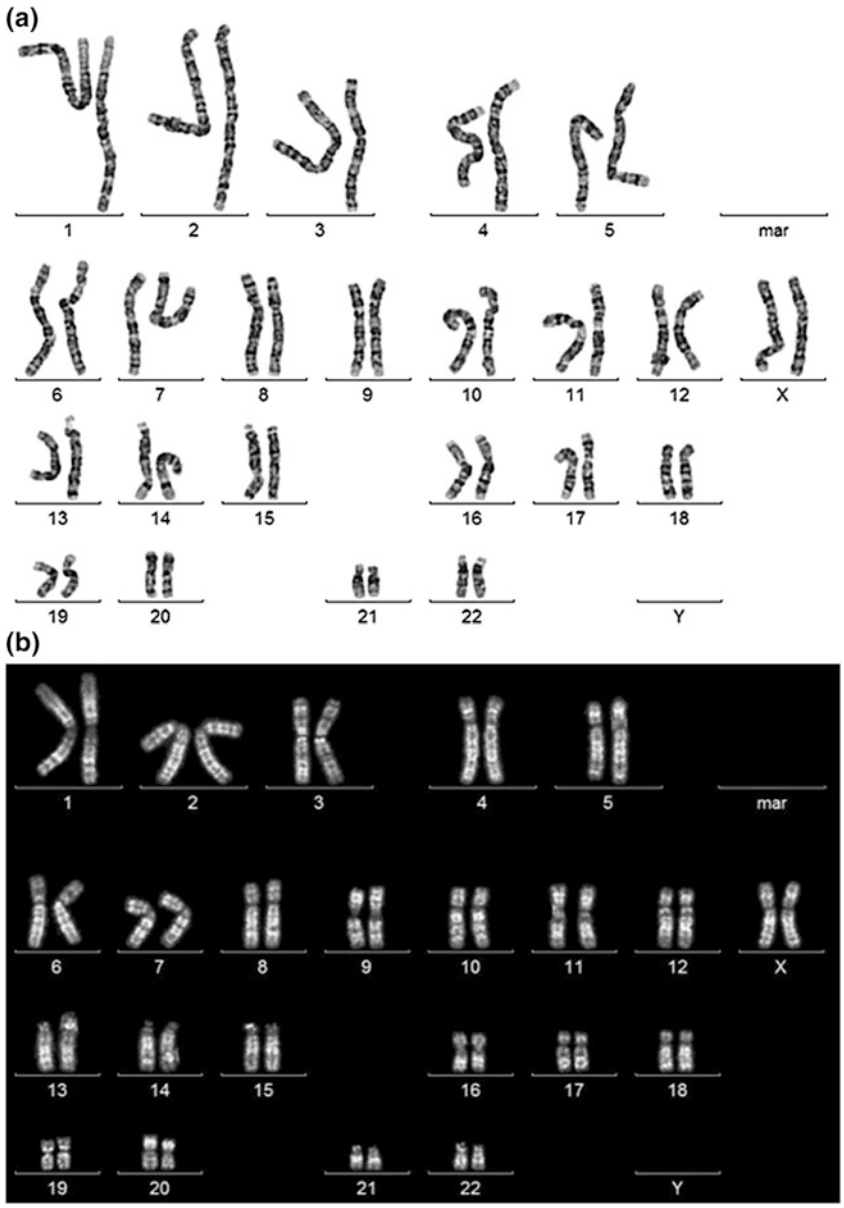

Fig. 4.61 Karyotype 46,XX,dup(9)(p11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal chromosomes 9, *right* derivate 9, **f** ideograms of chromosome 9; *left* normal, *right* duplicated chromosome, small interstitial duplication

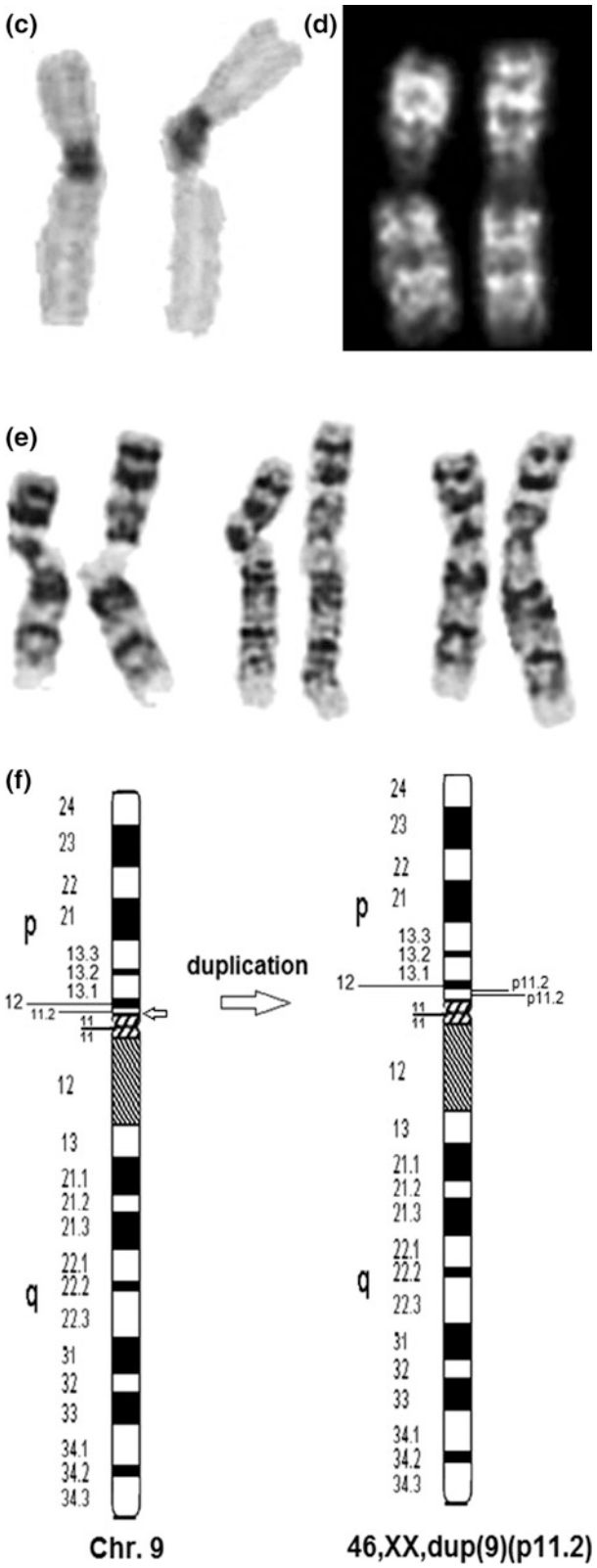

Fig. 4.61 (continued)

Case 2: Karyotype: 46,XY,dic(9)(pter→q11::p12→qter)
Indication for chromosome analysis: Gonosomal abnormality suspected.

Morphology:

Dicentric chromosome 9 with inactivation of the second centromere. The additional AT-rich band proximal in the long arm comprises furthermore a pericentromeric region with the second centromere inactivated. The additional region is located in the middle of the heterochromatic block q12. The additional segment is CBG-negative. The inactivation of the second centromere seems to be stable, as no malsegregation of the aberrant chromosome 9 was observed. Additional FISH investigations after microdissection is indicated.

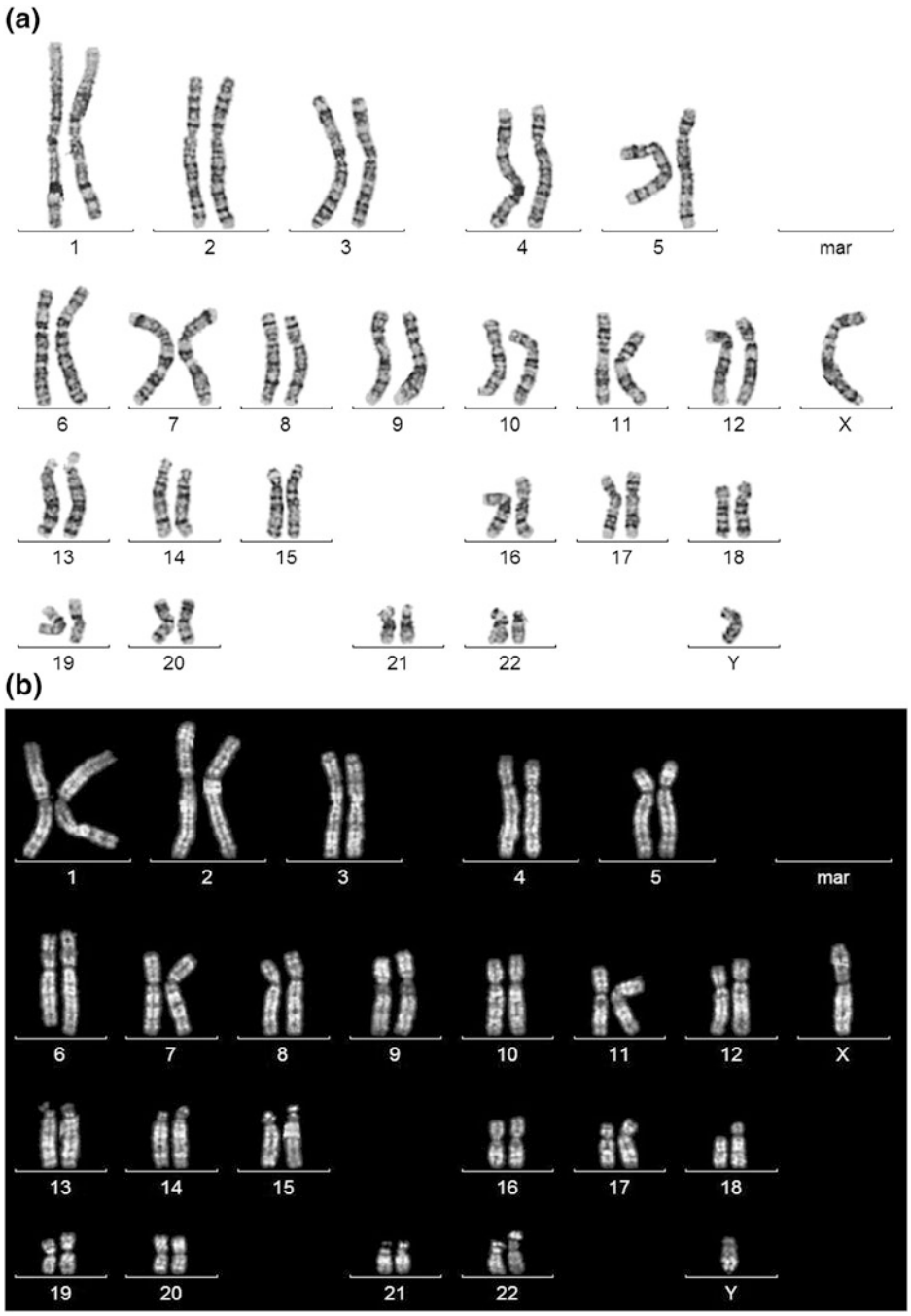

Fig. 4.62 Karyotype 46,XY,dup(9),dic(9)(pter→q11::p12→qter). Single pathologic cell with deletion of the short arm of chromosome 18. **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosome 9, **f** ideograms of chromosome 9; *left* normal, *right* duplicated chromosome, small interstitial duplication

Cave:

The minor anomalies of the patient are a problem when counseling the family as the genetic risk is less than 1% and due to the almost normal phenotype indication for prenatal investigation is questionable (Fig. 4.62).

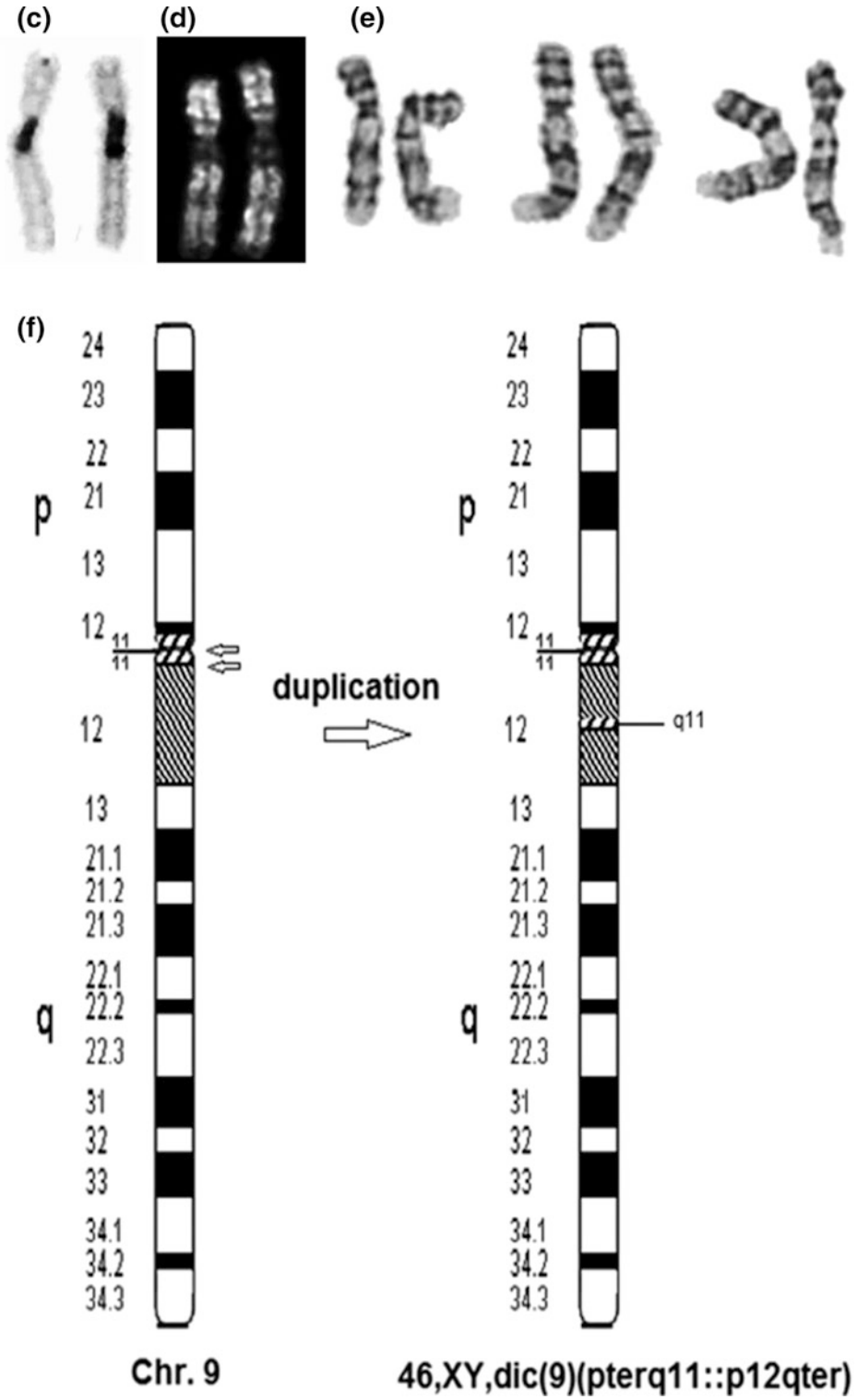

Fig. 4.62 (continued)

Case 3: Familial Duplication

Mother: Karyotype: 46,X,dup(X)(p11.4p21.2)
Son: Karyotype: 46,dup(X)(p11.4p21.2)y

Indication for chromosome analysis: congenital abnormalities in the son especially ambiguous genitalia.

Morphology:

The additional band in Xp is AT-rich and identic in both mother and son. It involves about 5% of the total length of the X-chromosome. The proximal banding pattern in Xp shows characteristic differences to the normal one.

Cave:

Prenatal diagnosis has to be offered to the consultant to exclude partial additional duplications or deletions in the conceptus, and in female fetuses the inactivation pattern of normal and aberrant X-chromosome should be analysed (Fig. 4.63).

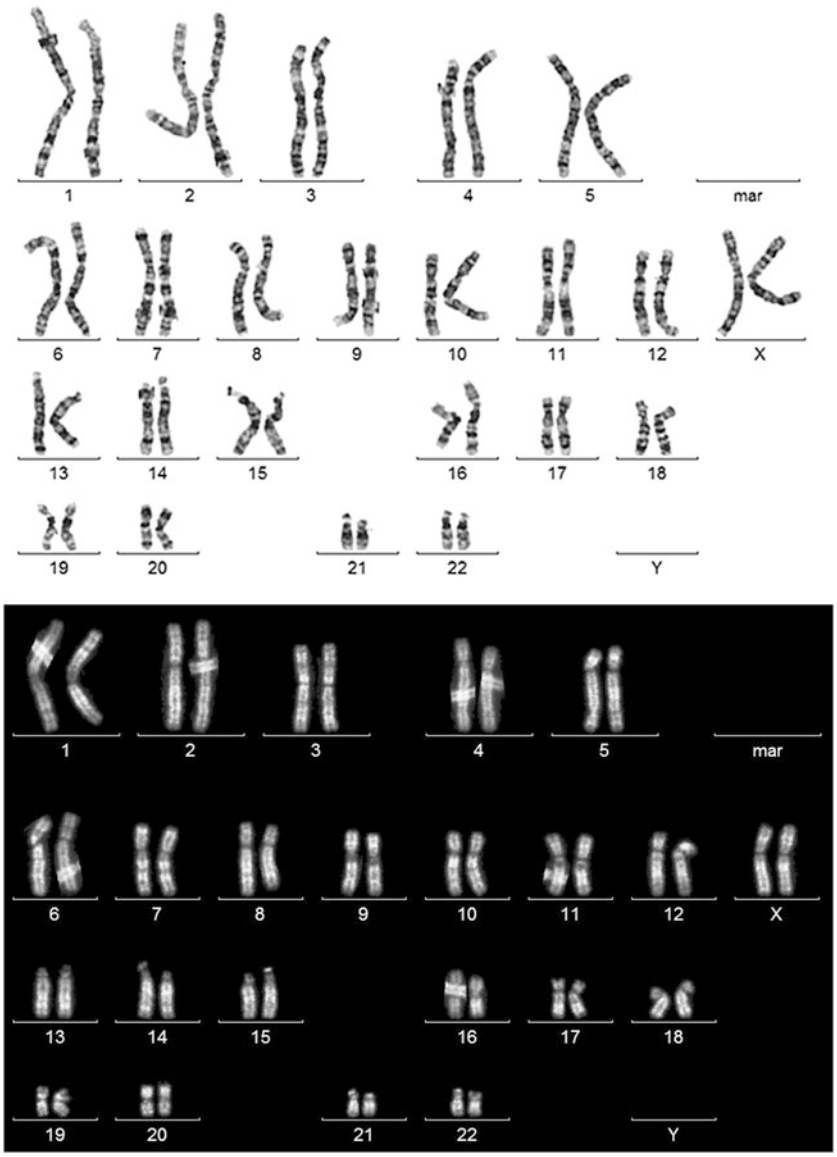

Fig. 4.63 Karyotype 46,X,dup(X)(1.4p21.2). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosome X, **e** ideograms of the X-chromosome, proximal duplication in the short arm

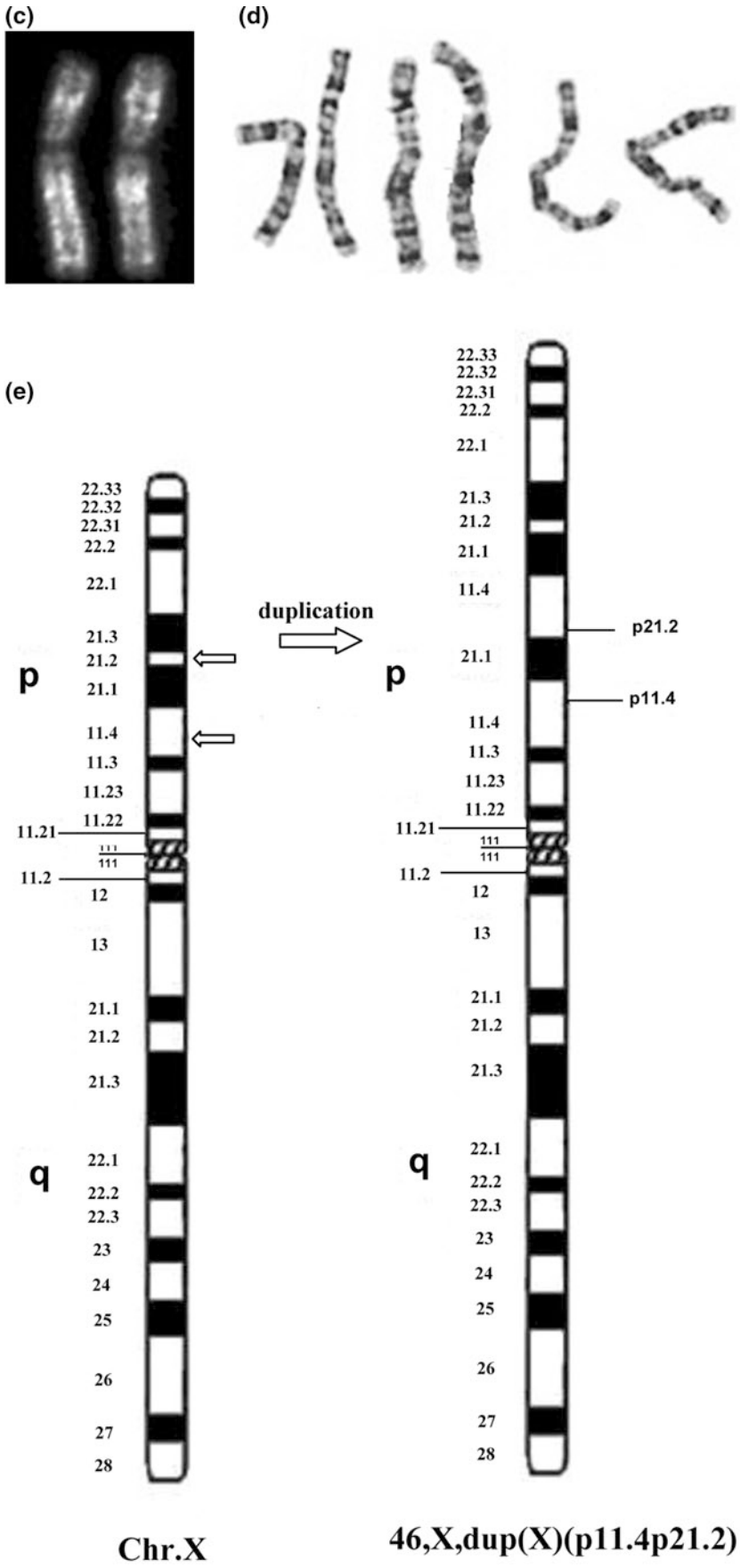

Fig. 4.63 (continued)

Summary
Three cases are presented, two autosomal duplications, two involving chromosome 9 and one gonosomal with abnormality of Xp. The duplication 9p12 is defined as a euchromatic variant without genetic risk. But it must be guaranteed that no neighboring euchromatic, genetic relevant segments are involved in the duplication. The second case shows a complex chromosome rearrangement resulting in a dicentric chromosome 9. The inactivation of the second centromere is complete; a second cell line is not present. The third case, a partial duplication of the short arm of the X-chromosome leads to a normal phenotype and fertility in the female carrier but to a malformation syndrome in the hemizygote son. The relevance of a screwed X inactivation in female carriers of an X abnormality must always be taken into account when counseling carriers and their relatives.

4.2.1.4 Ring Chromosomes

1 46,XX,r(18)(p11.23q21.33)
2 mos45,X[25]/46,X,r(X)(p22.1q21)[29]
3 46,X,r(Y)(p11.32q11.21)

Case 1: Karyotype: 46,XX,r(18)(p11.23q21.33)
Indication for chromosome analysis: Developmental retardation, morphologic peculiarities according to de Grouchy syndrome II.

Morphology:

The size of the ring chromosome is not identic in all metaphases analysed, part of the mitoses show a duplication of the ring. This abnormality is caused by a pathologic course of replication of the ring (S-phase).

Cave:

A mosaic karyotype of the patient with malsegregation of the ring has to be excluded. The chromosomes of the parents should be analysed before genetic counseling to exclude a balanced rearrangement (inversion) or a low grade mosaic (Fig. 4.64).

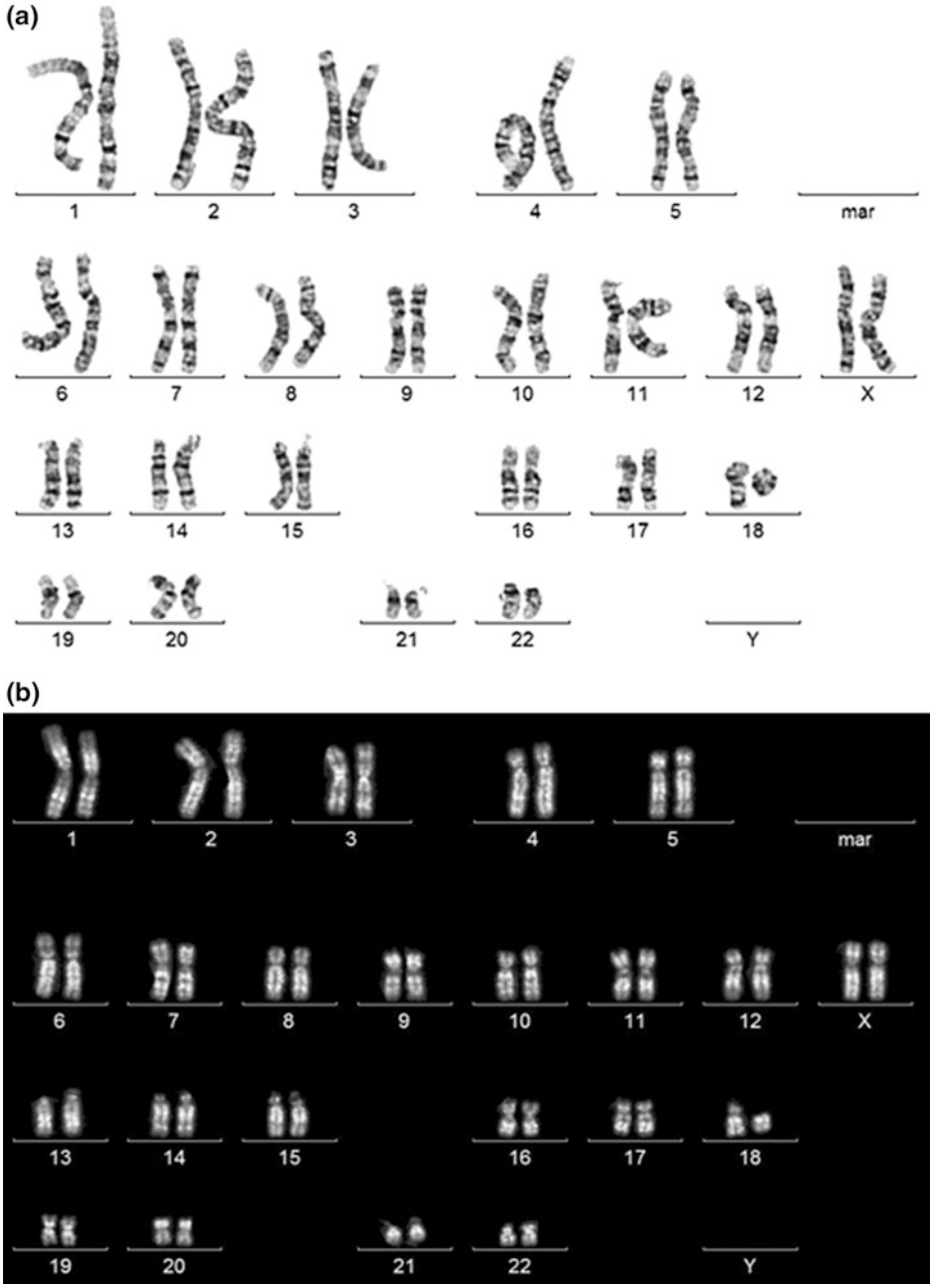

Fig. 4.64 Karyotype 46,XX,r(18)(p11.23q21.33). **a** GTG-, **b** QFQ-banding, 500 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, showing the ring in different positions and a duplication in 2 of them; chromosomes from different mitoses, **d**, **e** *left* normal, *right* ring chromosome 18, **f** ideograms and schematic illustration of the ring formation of chromosome 18. The presentation is completed by the findings after microarray analysis

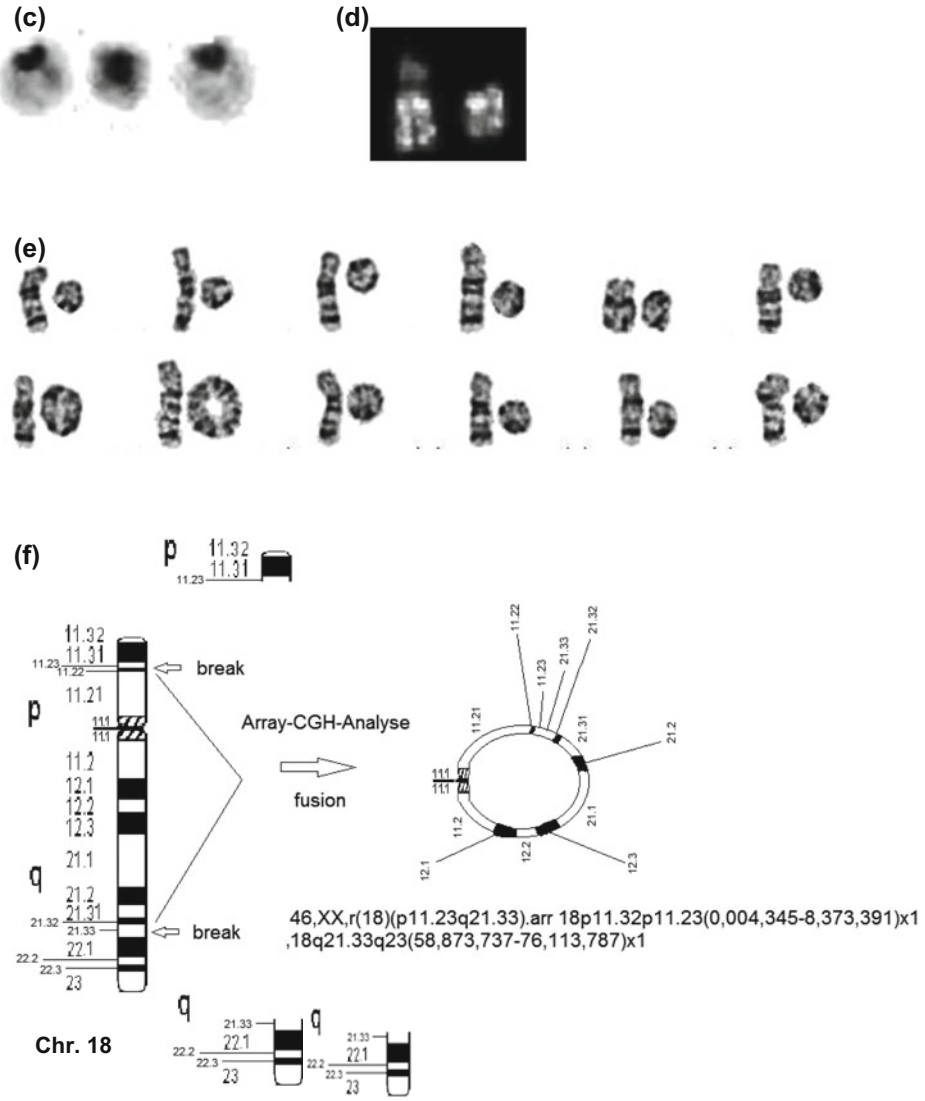

Fig. 4.64 (continued)

Case 2: Karyotype: mos45,X[25]/46,X,r(X)(p22.1q21)[29]
Indication for chromosome analysis: Turner syndrome.

Morphology:

The breakpoints can be localised in the distal region of the short arm and in the middle of the long arm, thus comprising about 38% of the total length of the X-chromosome. The ring is unstable in the course of cell divisions and got lost in about 50% of the mitoses analysed. Besides, partial and complete duplications of the ring by abnormalities of chromosome replication (S-phase of the cell cycle) were documented.

Cave:

Prognosis and therapy of the patient will be performed as in monosomy X cases without an additional structural aberration (Fig. 4.65).

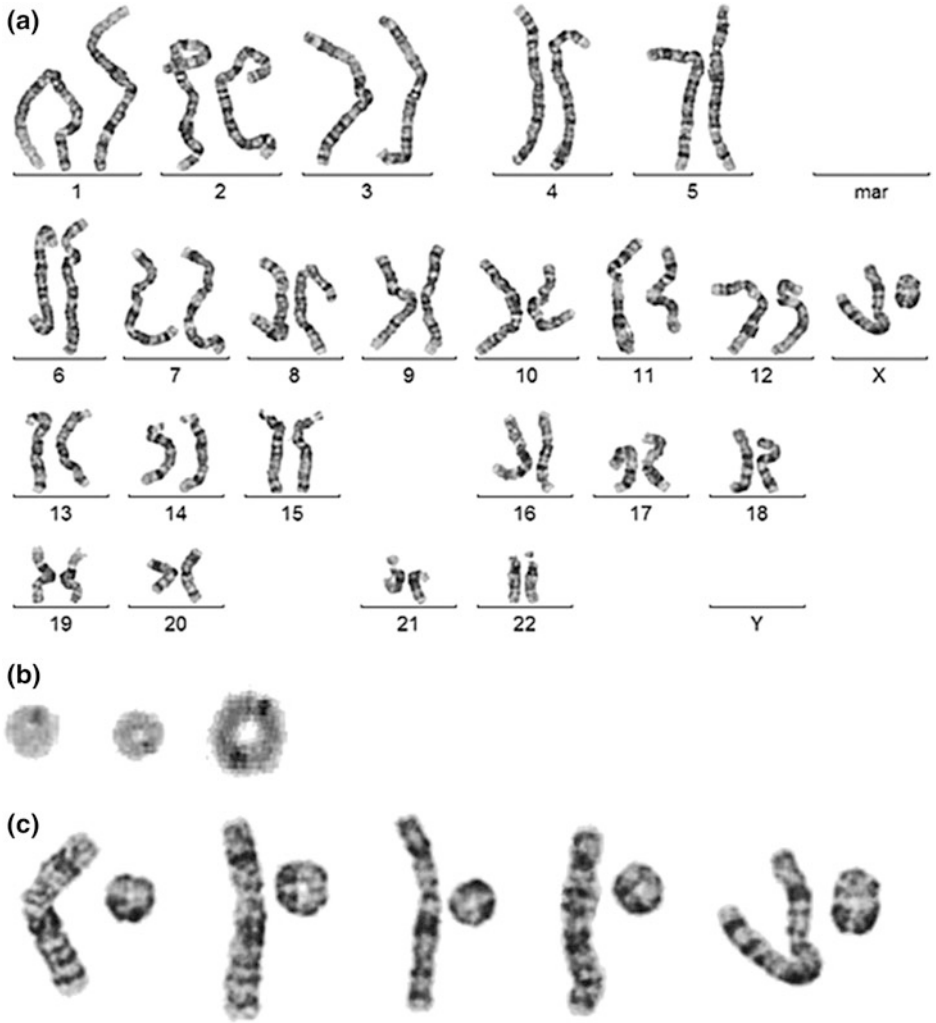

Fig. 4.65 **a** Karyotype 46,X,r(X)(p22.1q21), GTG-banding, 850 bands per genome, **b** CBG-, **c** GTG-banding, **b** *right* figure shows a ring duplication, **c** *left* normal, *right* ring chromosome X, **d** ideograms of the X-chromosome with illustration of the ring formation

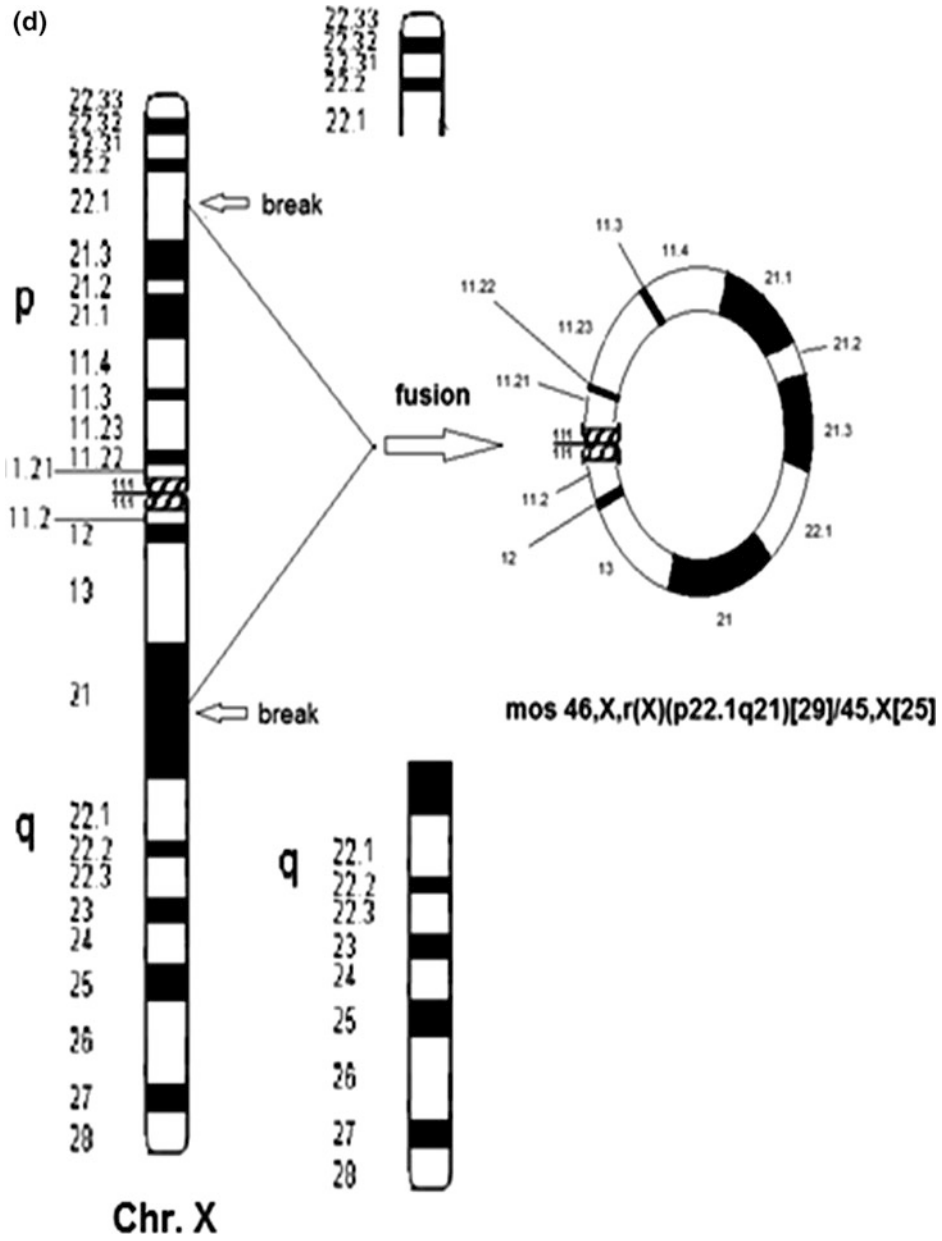

Fig. 4.65 (continued)

Case 3: Karyotype: 46,X,r(Y)(p11.32q11.21)
Indication for chromosome analysis: Male infertility.

Morphology:

The ring chromosome is characterised by the missing heterochromatic region (Yq12). The ring is stable in the course of cell divisions, therefore mosaic formation could be excluded.

Cave: none (Fig. 4.66).

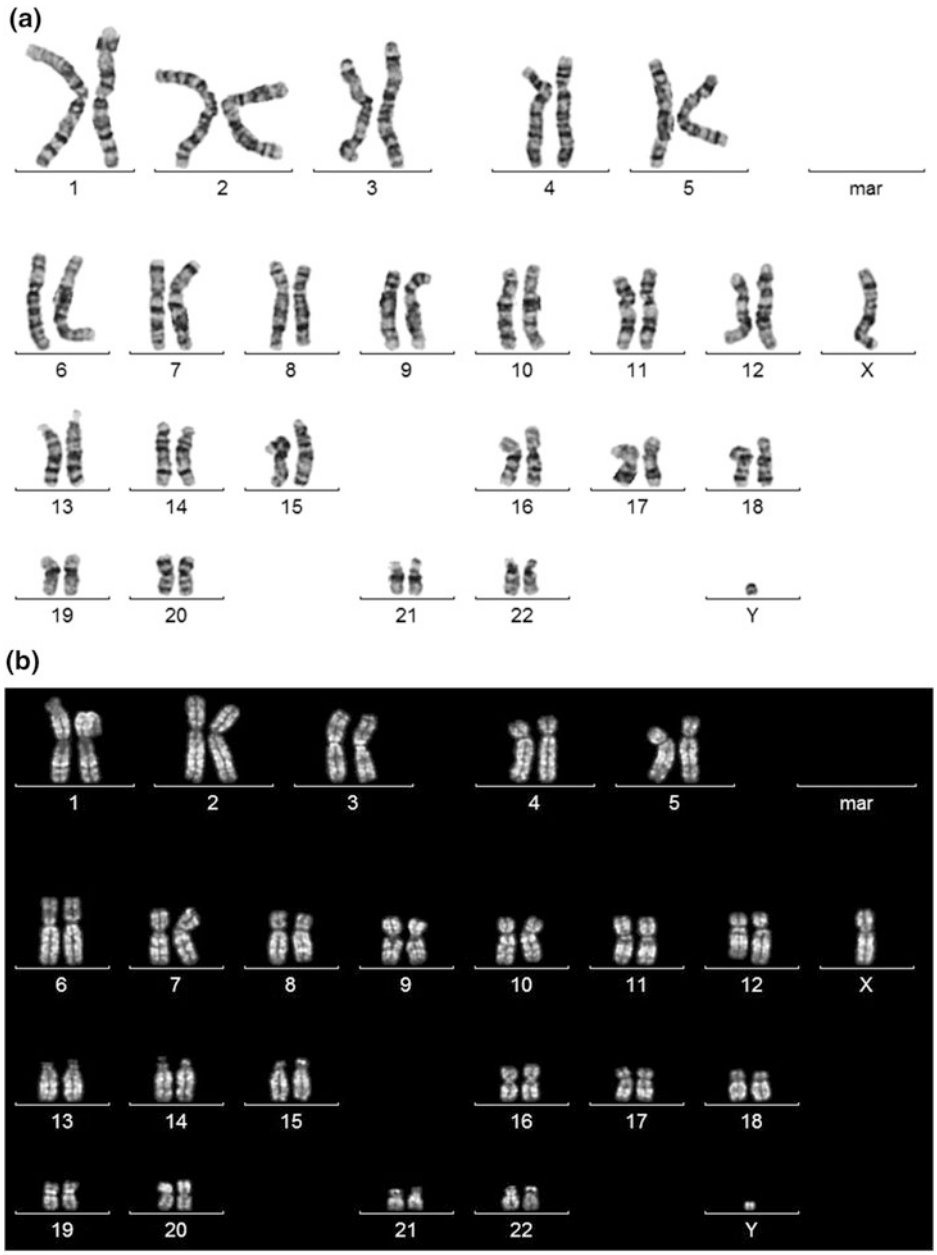

Fig. 4.66 Karyotype 46,X,r(Y)(p11.32q11.21). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** GTG-banding, chromosomes from different mitoses, duplicated ring, **d** ideograms of ring Y-chromosome with scheme of the ring formation

Summary

Three cases are described in detail, which make the problems clear when ring chromosomes must be analysed. Chromosomes 18, X, and Y are involved in ring formation. In all three cases additional investigations by FISH and microarray were necessary to define exactly the breakpoints. As in the present case of r(18) this aberration is, according to the literature, characterised by a frequently pathologic course of the cell cycle, especially the S-phase, were partial and complete duplications of the ring chromosome arise. In the second case of a ring chromosome X, the karyotype is characterised by a second cell line with monosomy X (45,X), which developed by loss of the ring chromosome in part of the cells. These secondary X0-mosaics are frequent observations in different types of structural aberrations of the X-chromosome. As in the first case of r(18) also in the patient with r(X) duplications of the ring chromosomes caused by replication errors were analysed. In the third case of a ring chromosome Y the ring was stable inherited by the somatic cell divisions. Duplications of the ring were not observed. But from the literature it is well known that a cell line with monosomy X as well as partial and complete duplications of r(Y) can occur.

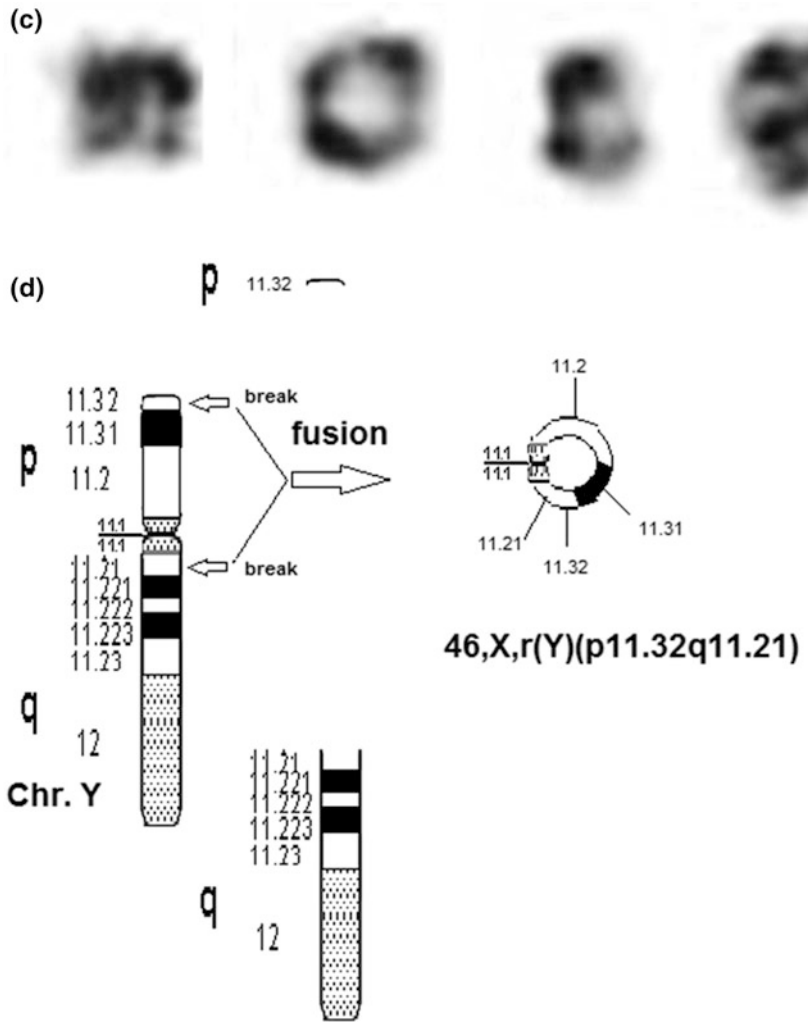

Fig. 4.66 (continued)

The three cases presented here, make it obvious, that in all cases of ring chromosomes at least 50 mitoses have to be analysed, to find out if the carrier presents with secondary mosaic formation by aneuploidisation and/or secondary structural aberrations. In cases of extremely instable ring chromosomes the indication for additional investigations of the complex karyotype might be given. These can be performed either by the analysis of a second somatic cell system or by the investigation of the same cell system after an interval of 1 or 2 years.

4.2.1.5 Isochromosomes

1 47,XY,+i(18)(q10)
2 46,XX,i(18)(q10)
3 46,X,i(X)(q10)
4 mos 45,X[26]/46,X,i dic(X)(p11.23)[24]
5 46,X,I dic(Y)(q11.23)

Case 1: Karyotype: 47,XY,+i(18)(q10)
Indication for chromosome analysis: Developmental retardation, minor facial dysmorphisms.

Morphology:

The additional isochromosome shows a characteristic structure. Only in the presence of a second centromere the existence of a second cell line without the isochromosome that is with normal karyotype, has to be taken into account. The frequency of this aberration is about 1:45.000.

Cave:

The majority of additional isochromosomes 18 are de novo and paternal in origin. A few familial cases have been published. Therefore chromosome investigations in the parents should be performed before genetic counseling (Fig. 4.67).

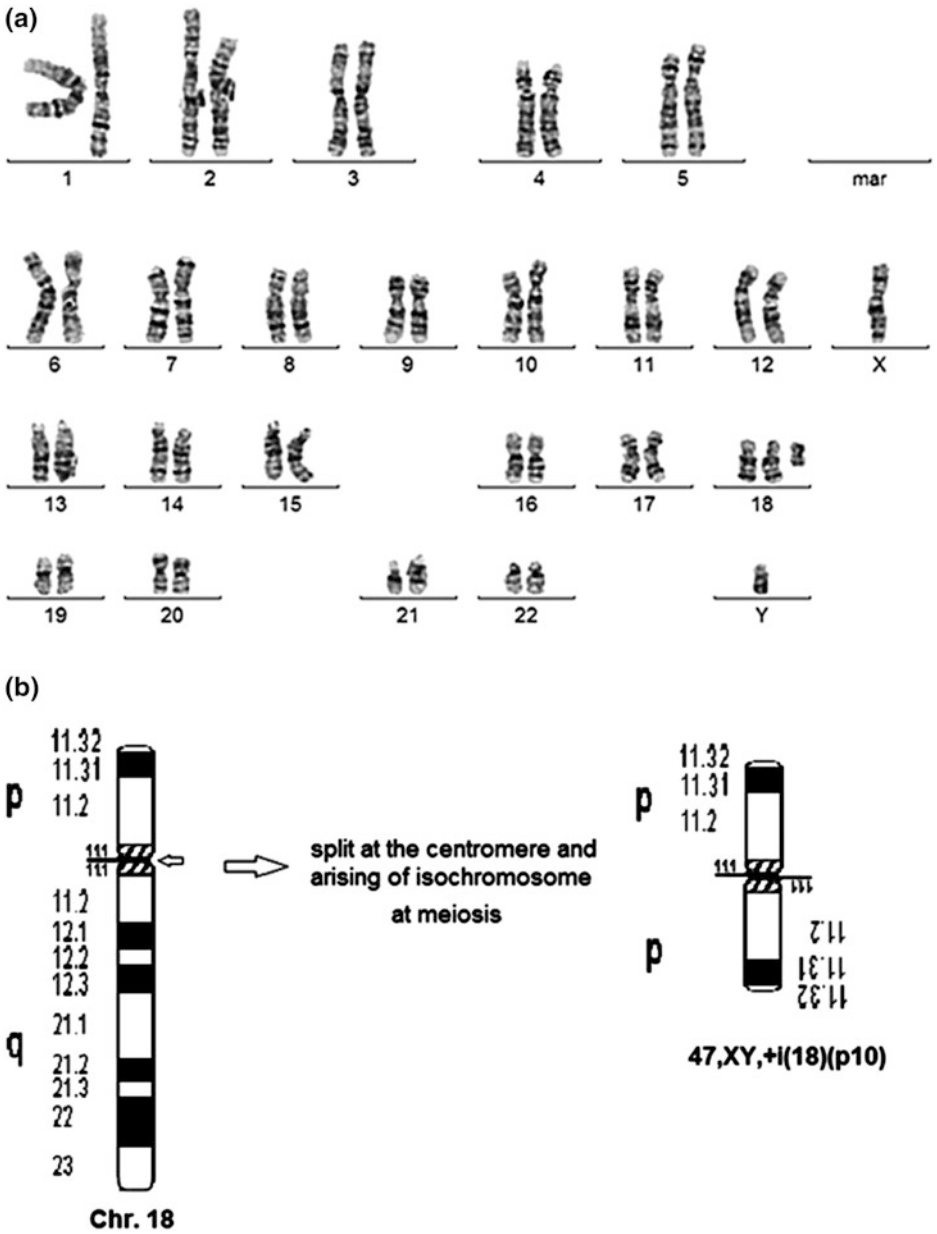

Fig. 4.67 **a** Karyotype 47,XY,+i(18)(q10), GTG-banding, 500 bands per genome, **b** ideograms of normal and aberrant chromosomes 18; aneuploidy by additional isochromosome 18p or tetrasomy 18p, *left* normal, *right* isochromosome p

Case 2: Karyotype: 46,XX,i(18)(q10)

Indication for chromosome analysis: Prenatal growth retardation, severe malformations, mild trisomy 18 features.

Morphology:

The aberrant structure i18q is so easy so recognize, that even a resolution of less than 550 bands per genome permits the analysis. This is relevant, as prenatal investigations after CVS are performed as the ultrasound shows early abnormalities of the conceptus. The frequency of the aberration is less than 1:90.000.

Cave:

Single familial cases have been observed, one with a parental inversion giving rise to the rearrangement. Before genetic counseling the parents should be investigated (Fig. 4.68).

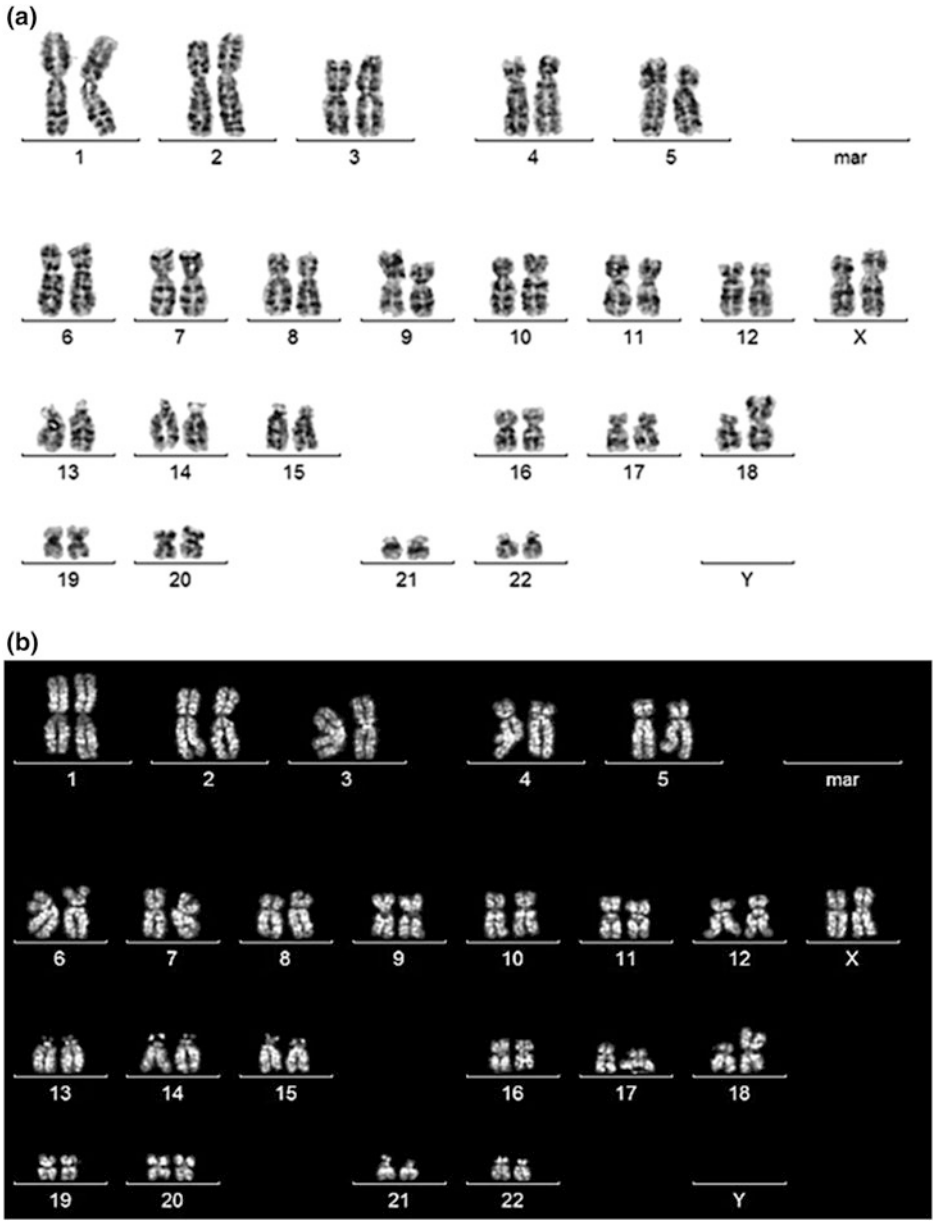

Fig. 4.68 Karyotype 46,XX,i(18)(q10) **a** GTG-, **b** QFQ- banding, each 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosome 18, **e** ideograms of normal and aberrant chromosomes 18, unbalanced rearrangement, *left* normal chromosome 18, *right* isochromosome q

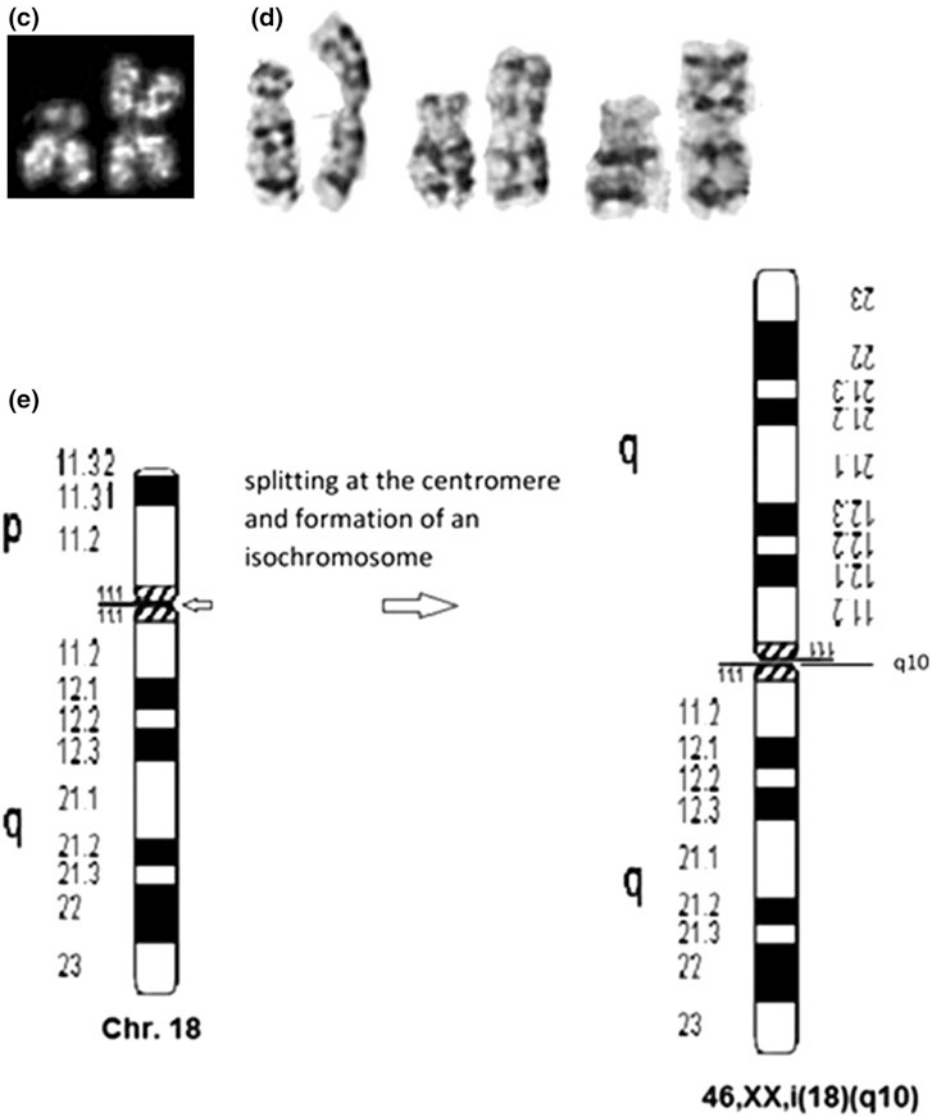

Fig. 4.68 (continued)

Case 3: Karyotype: 46,X,i(X)(q10)
Indication for chromosome analysis: Prenatal diagnosis because of increased maternal age (40 years).

Morphology:

The monocentric and metacentric isochromosome is consisting of the 2 long arms of the X-chromosome. This leads to a trisomy Xq and a monosomy Xp. The isochromosome with one centromere was inherited unchanged in the course of cell divisions.
Cave:

The child will show the phenotype of Turner syndrome (Fig. 4.69).

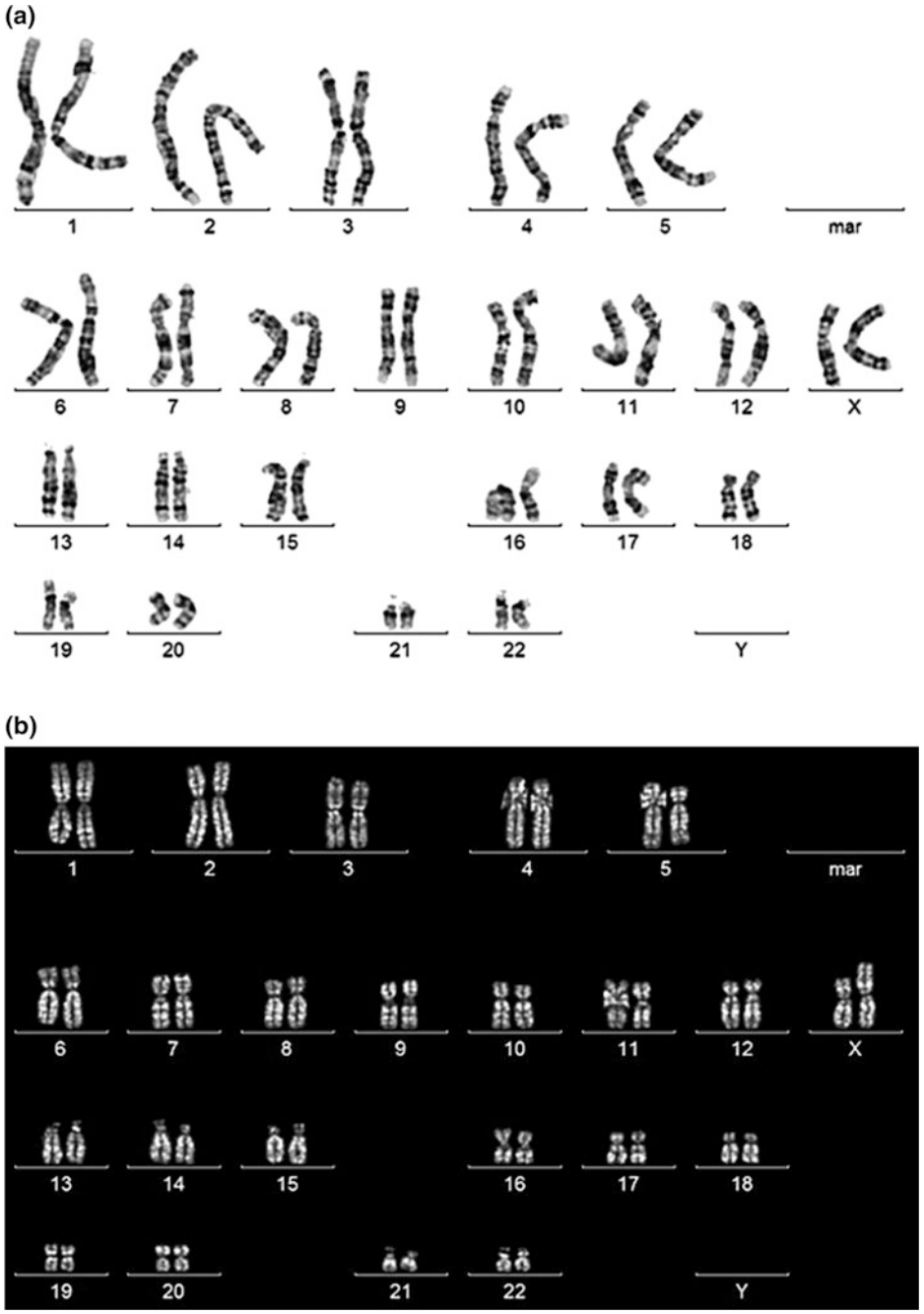

Fig. 4.69 Karyotype 46,X,i(X)(q10). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, **c** *left* normal, *right* aberrant X-chromosome, **e** ideograms of normal and aberrant X-chromosomes, unbalanced rearrangement, *left* normal, *right* isochromosome q

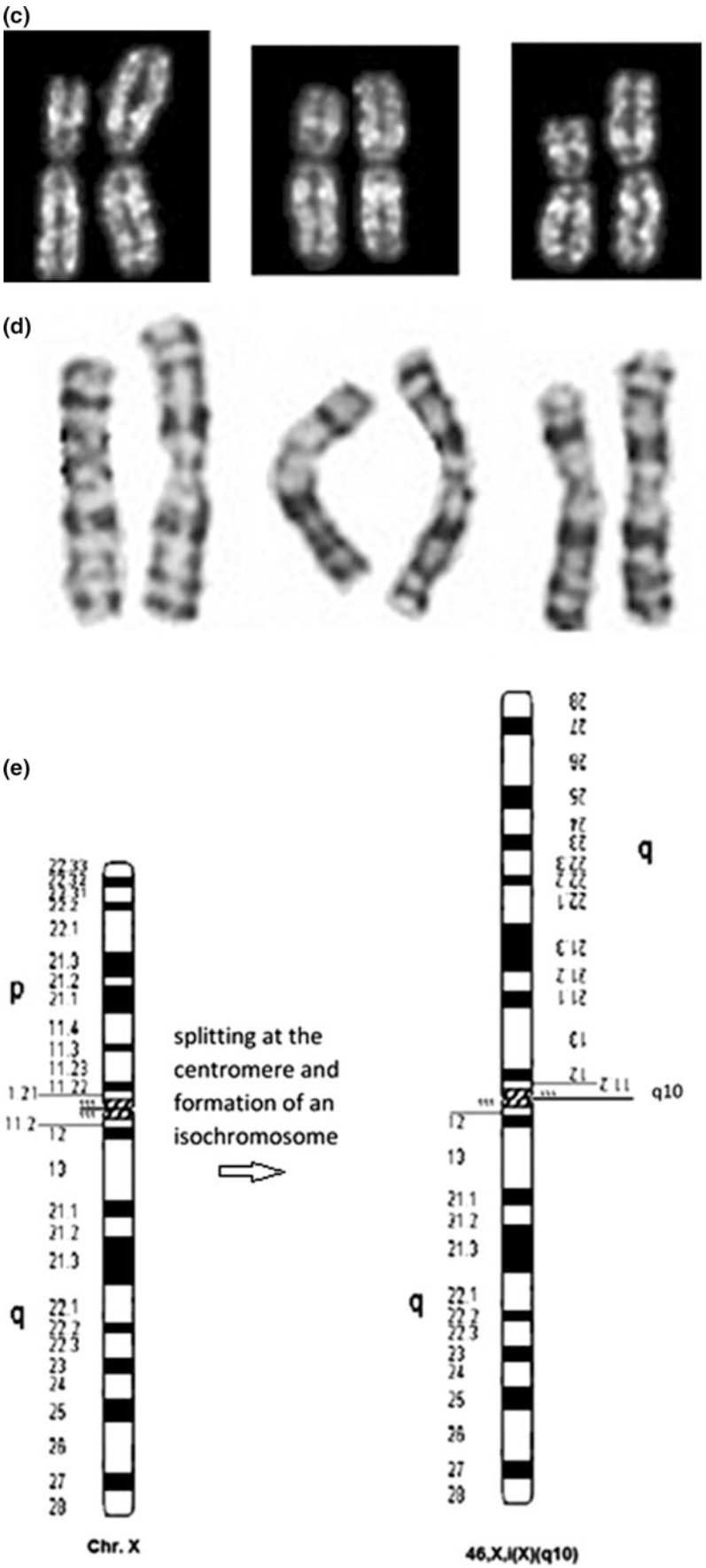

Fig. 4.69 (continued)

Case 4: Karyotype: mos 45,X[26]/46,X,i dic(X)(p11.23)[24]

Indication for chromosome analysis: Developmental retardation of a 7 years old girl.

Morphology:

The isochromosome X is dicentric with breakpoint in the proximal part of the short arm. The inactivation of the second centromere (see also C-banding) is incomplete leading to a second cell line with monosomy X.

Cave:

The characteristic phenotype of Turner syndrome is often not recognizable in young girls. But to the parents the prognosis has to be explained and especially the given possibilities of therapy have to be discussed (Fig. 4.70).

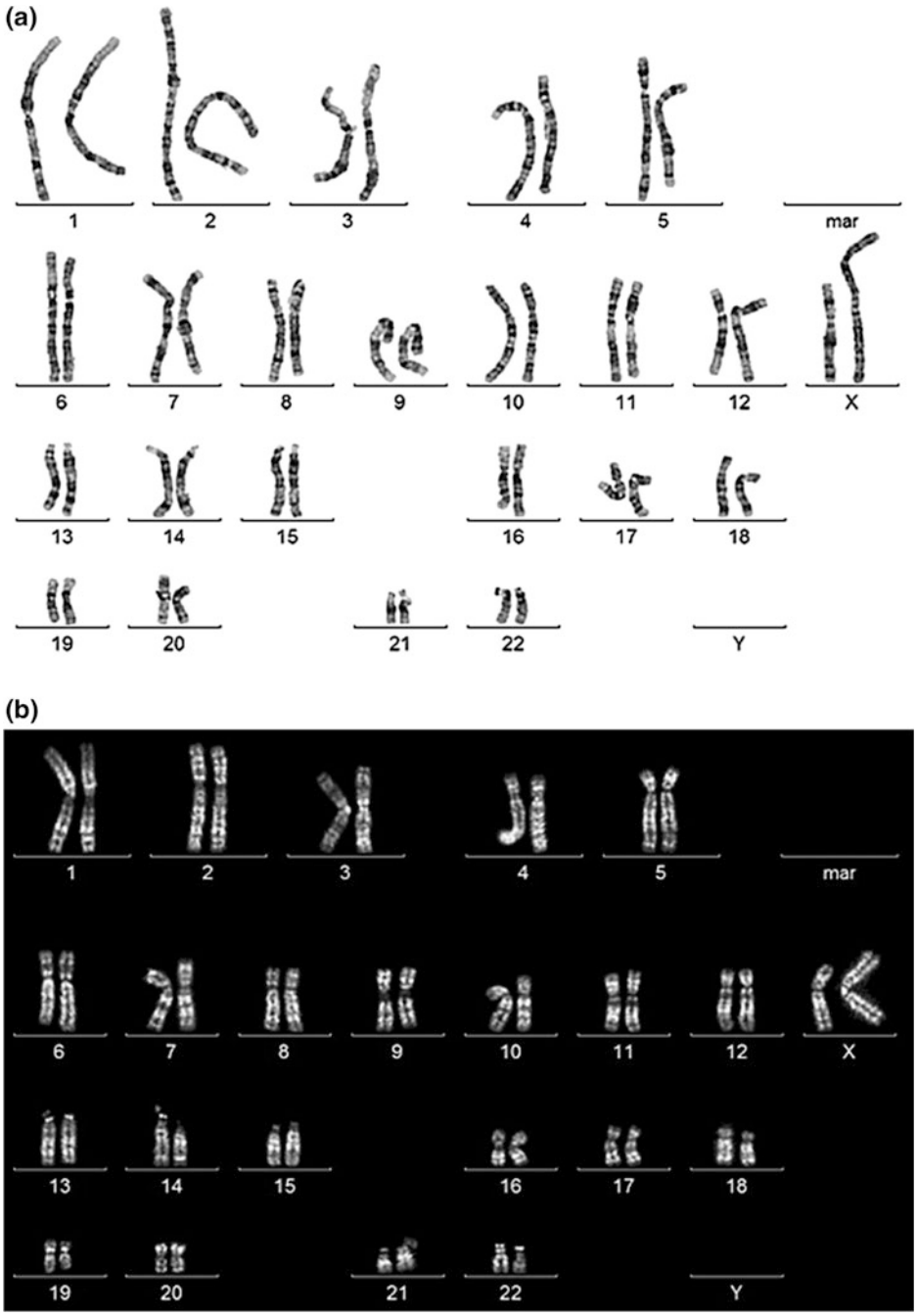

Fig. 4.70 Karyotype mos 45,X[26]/46,X,idic(X)(p11.23)[24]. **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant X-chromosome, **f** ideograms of the X-chromosome deletion of the short and duplication of the long arm. Breakpoint in the proximal short arm, resulting in a dicentric derivate

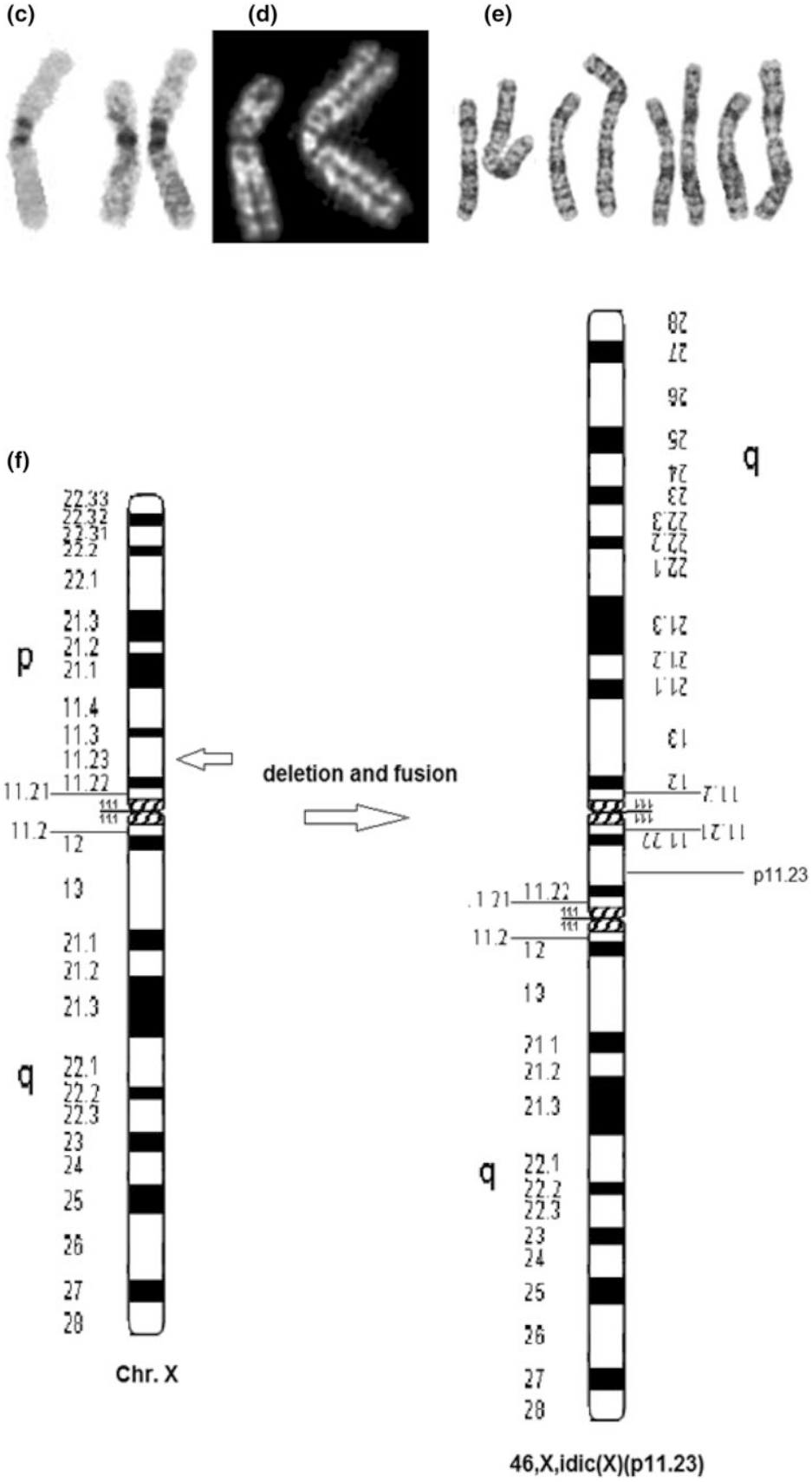

Fig. 4.70 (continued)

Case 5: Karyotype: 46,X,i dic(Y)(q11.23)
Indication for chromosome analysis: Azoospermia.

Morphology:

The aberrant Y-chromosome is dicentric with breakpoint in the distal part of the long arm (q11.23). The inactivation of the second centromere is complete, no further cell line was observed.

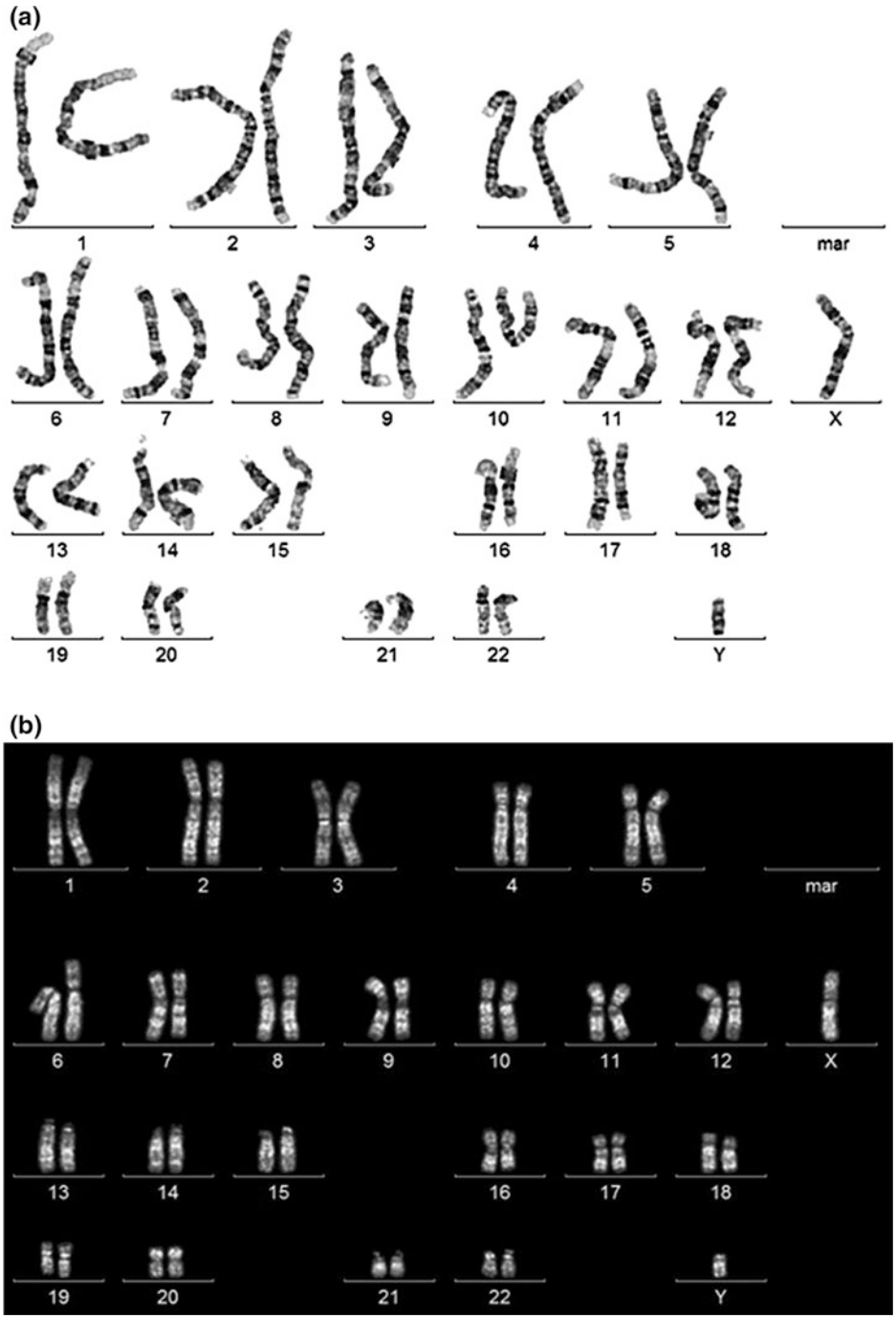

Fig. 4.71 Karyotype 46,X,i dic(Y)(q11.23). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, d/1: normal Y-chromosome from a control person, aberrant Y-chromosome with 1 centromere inactivated, **f** ideograms of the Y-chromosome, deletion of the terminal long arm and duplication of the short and proximal long arm, one centromere inactivated

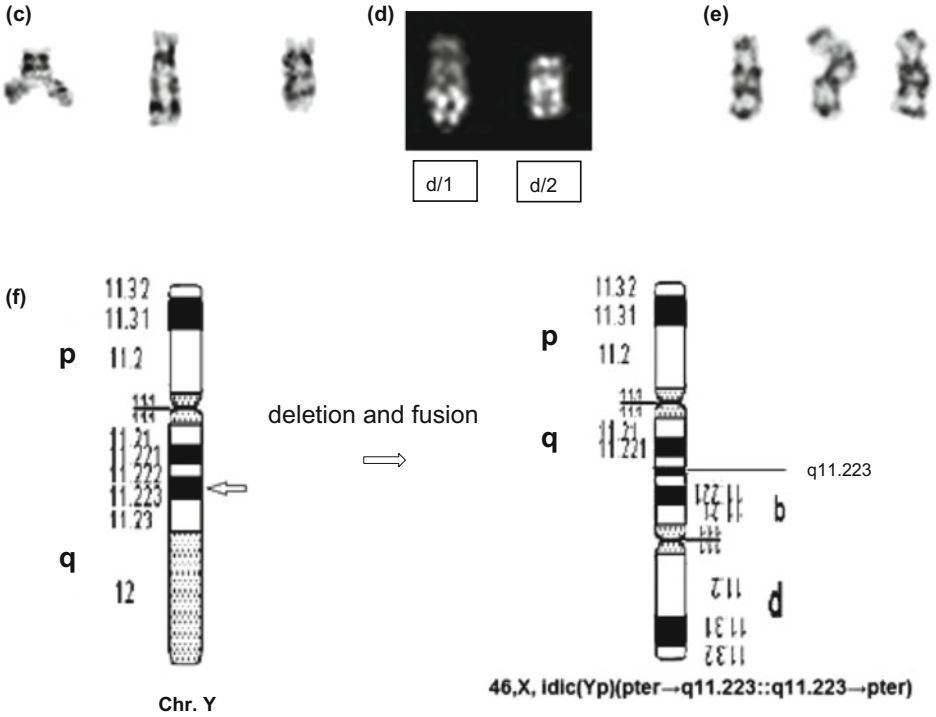

Fig. 4.71 (continued)

Cave:

Additional molecular investigations revealed deletions of sY254, sY255 and the AZFc-region (Fig. 4.71).

Summary

Exemplary five cases of isochromosomes—two of the autosomes and three of the gonosomes are presented in detail. These are two aberrations of chromosome 18, two of the X- and one of the Y-chromosome. The first case is an additional isochromosome of the short arms of chromosome 18. This type of supernumerary derivate 18 is a frequent abnormality, of which about 100 cases have been reported. This isochromosome is usually monocentric and thus stable inherited by mitoses. The second case is an isochromosome of the long arms of chromosome 18, again monocentric and stable when inherited. The chromosome number is 46, thus it combines a monosomy 18p with trisomy 18q. As it leads to a severe malformation complex in the carrier, life expectancy is significantly reduced. The third case concerns a monocentric isochromosomes X of the long arms (q). This is a frequent structural aberration of the X-chromosome. Monocentric isochromosomes X are in the majority of cases stable in mitosis, in contrast to dicentric rearrangements. The development of mosaicism by a second cell line with the karyotype 45,X has not to be expected. But this feature was observed in the second case of chromosome X aberration presented here, where the dicentric isochromosome X with breakpoint in Xp11.23 leads to the formation of a second cell line with karyotype 45,X. The reason for this instability is the incomplete inactivation of the second centromere. In the last case a dicentric Y-chromosome is presented with breakpoint in the distal euchromatic region of the long arm (Yq11.23). By CBG-banding it was clearly analysable that the second centromere is always completely inactivated. Therefore this isochromosome is stable inherited during mitoses. A second cell line does not exist.

The cases presented here, make it obvious, that the inactivation of centromeres in dicentric chromosomes can lead to a defect in the process of the cell cycle and therefore always must be analysed by CBG-banding. If abnormalities of inactivation are stated, at least 50 mitoses have to be analysed, to find out if quantitative and qualitative changes of the karyotype exist, caused by mosaic formation.

4.2.2 Interchromosomal Rearrangements

4.2.2.1 Translocations

Reciprocal Translocations

1 46,XY,t(2;18)(p25.3;p11.2)
2 46,XX,t(4;16)(q31.3;q13)
3 46,XX,t(9;11)(q11;p11.2)
4 46,XY,der(9),t(9;12)(p24.3;q24.13)
arr 12q24.13q24.33(114,023,119-133,773,499)x3 de novo
5 46,XX,t(11;22)(q23.3;q11.2)
6 46,XX,t(12;18)(q10;p11.2)
7 45,XY,der(18),t(18;22);(p11.32;q11.2),-22
8 46,X,t(X;6)(q26.1;p25.1)
9 46,X,t(Y;5)(q11.21;p15.33)

Case 1: Karyotype: 46,XY,t(2;18)(p25.3;p11.2)
Indication for chromosome analysis: 5 handicapped children (see pedigree).

Morphology:

The 2 translocation chromosomes are not easy to identify as the exchanged regions are small. This requires a high banding resolution for identification (at least 700 bands/genome) and in prenatal diagnosis an additional microarray investigation is required.
Cave:

The phenotype of the carriers of the same type of unbalanced translocation is different in the severity of clinical symptoms. Thus a prognosis during the prenatal period must include this restriction (Fig. 4.72).

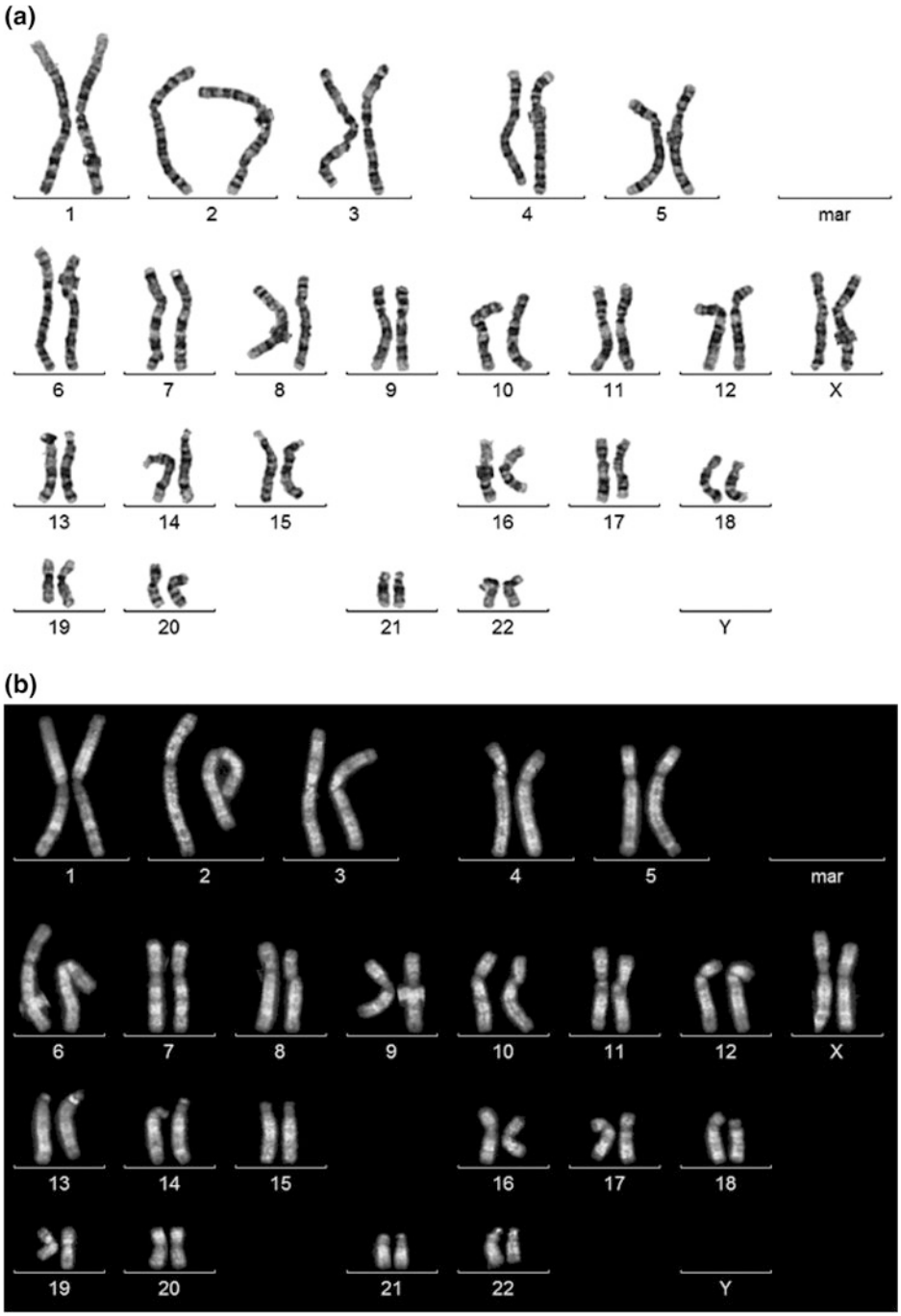

Fig. 4.72 Karyotype 46,XY,t(2;18)(p25.3;p11.2). **a** GTG-, **b** QFQ-banding, 600 and 500 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosomes 2 and 18, **e** ideograms of normal and aberrant chromosomes 2 and 18, balanced translocation, **f** Pedigree showing the inheritance of 2/18 translocation in 4 generations of the family

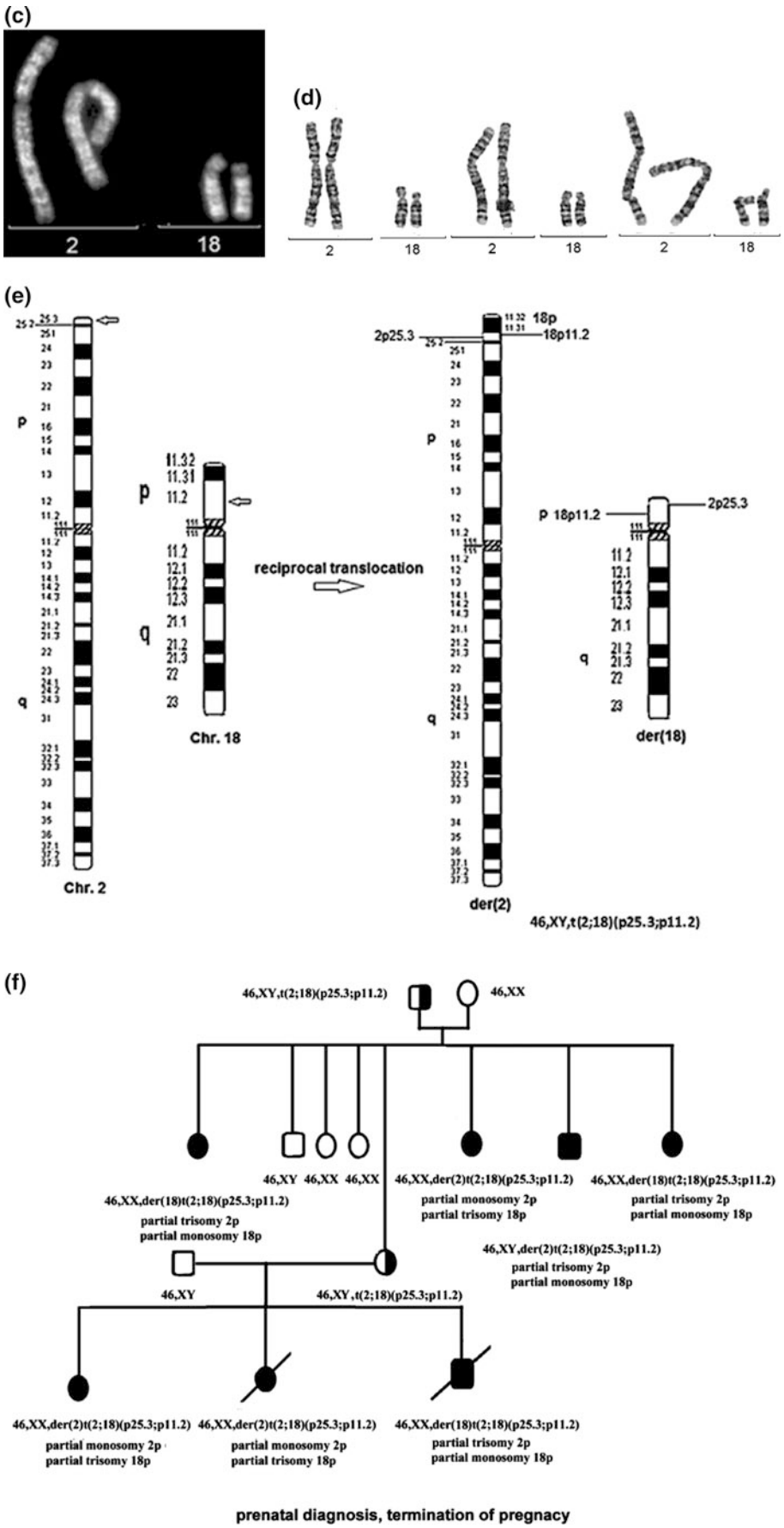

Fig. 4.72 (continued)

Case 2: Karyotype: 46,XX,t(4;16)(q31.3;q13)
Indication for chromosome analysis: Sterility.

Morphology:

The regions exchanged comprise about 20% (chromosome 4) and 30% (chromosome 16) of the 2 translocation chromosomes. Thus they can be easily recognised by their changed size and altered centromere index. For exact localisation of the breakpoints a banding resolution of at least 700 bands per genome is recommended.

Cave:

Family investigations should be offered (Fig. 4.73).

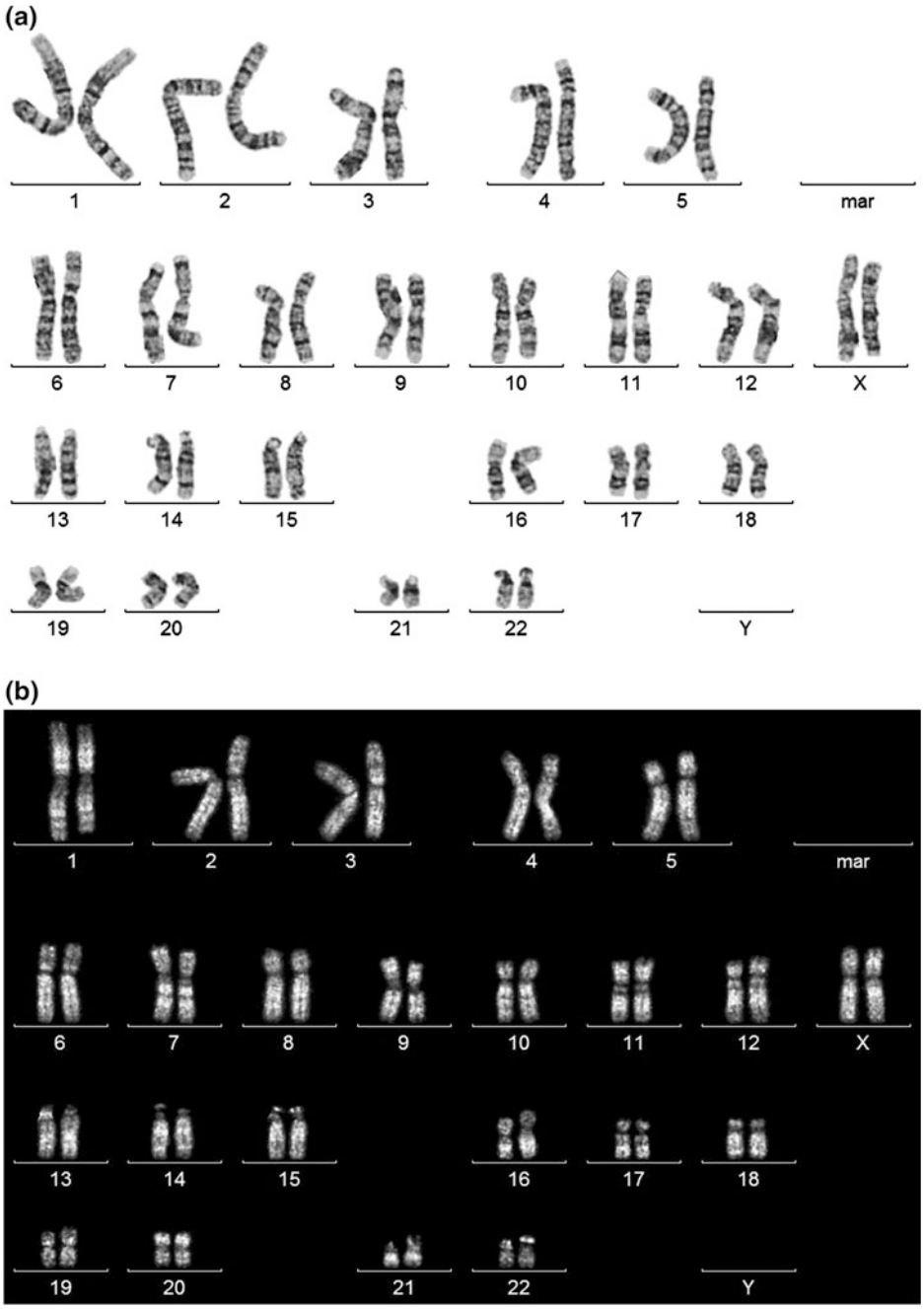

Fig. 4.73 Karyotype 46,XX,t(4;16)(31.3;q13). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosomes 4 and 16, **e** ideograms of normal and aberrant chromosomes 4 and 16, balanced translocation

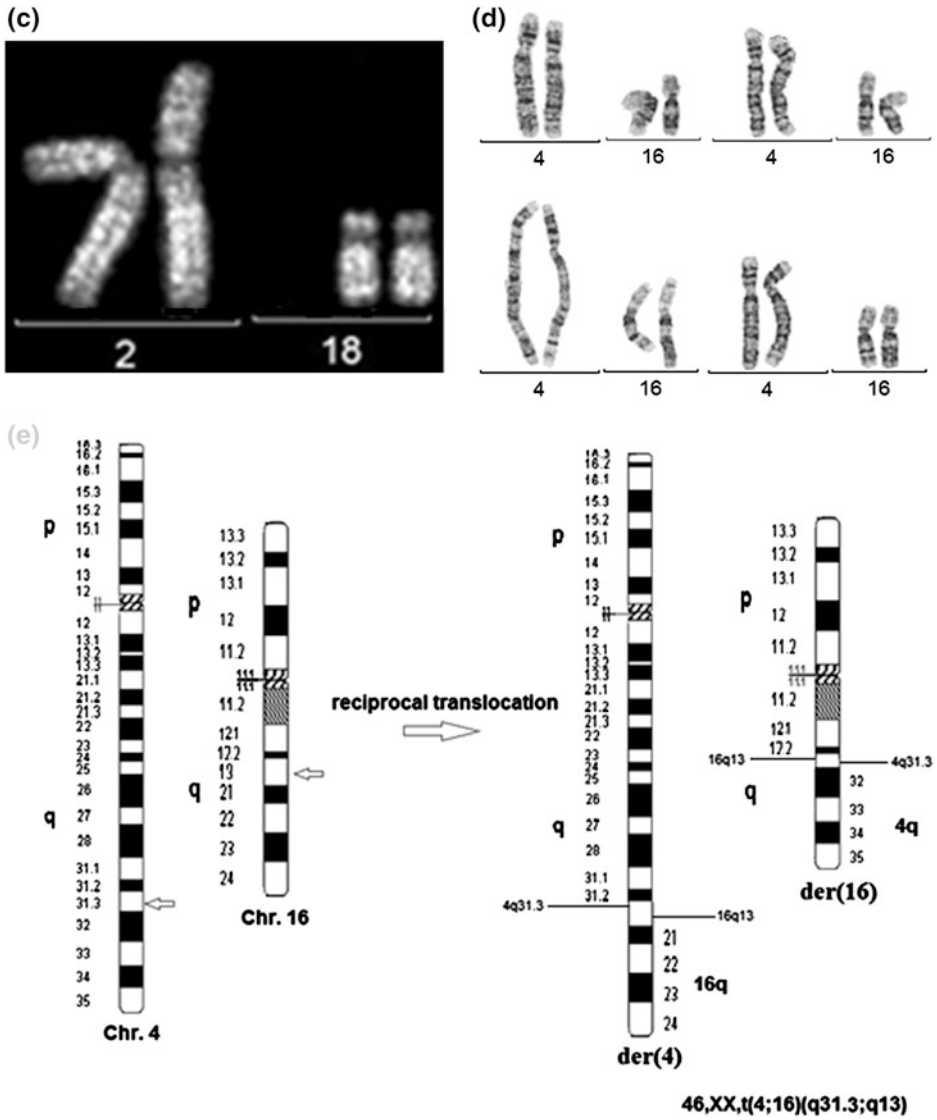

Fig. 4.73 (continued)

Case 3: Karyotype: 46,XX,t(9;11)(q11;p11.2) ish t(9;11)(cep9+;cep11+)
Indication for chromosome analysis: Known familial rearrangement before polar body analysis.

Morphology:

The translocation is easy to analyse by the dislocation of 9q12 into the proximal region of 11p (see C-banding) and by the changed size and centromere index of the translocation chromosomes, which both appear almost metacentric. The size of the regions exchanged is about 66% in chromosome 9 and 35% in chromosome 11.

Cave:

The risk of an unbalanced karyotype is increased by a possible malsegregation, i.e. aneuploidisation, of the smaller translocation chromosome (Fig. 4.74).

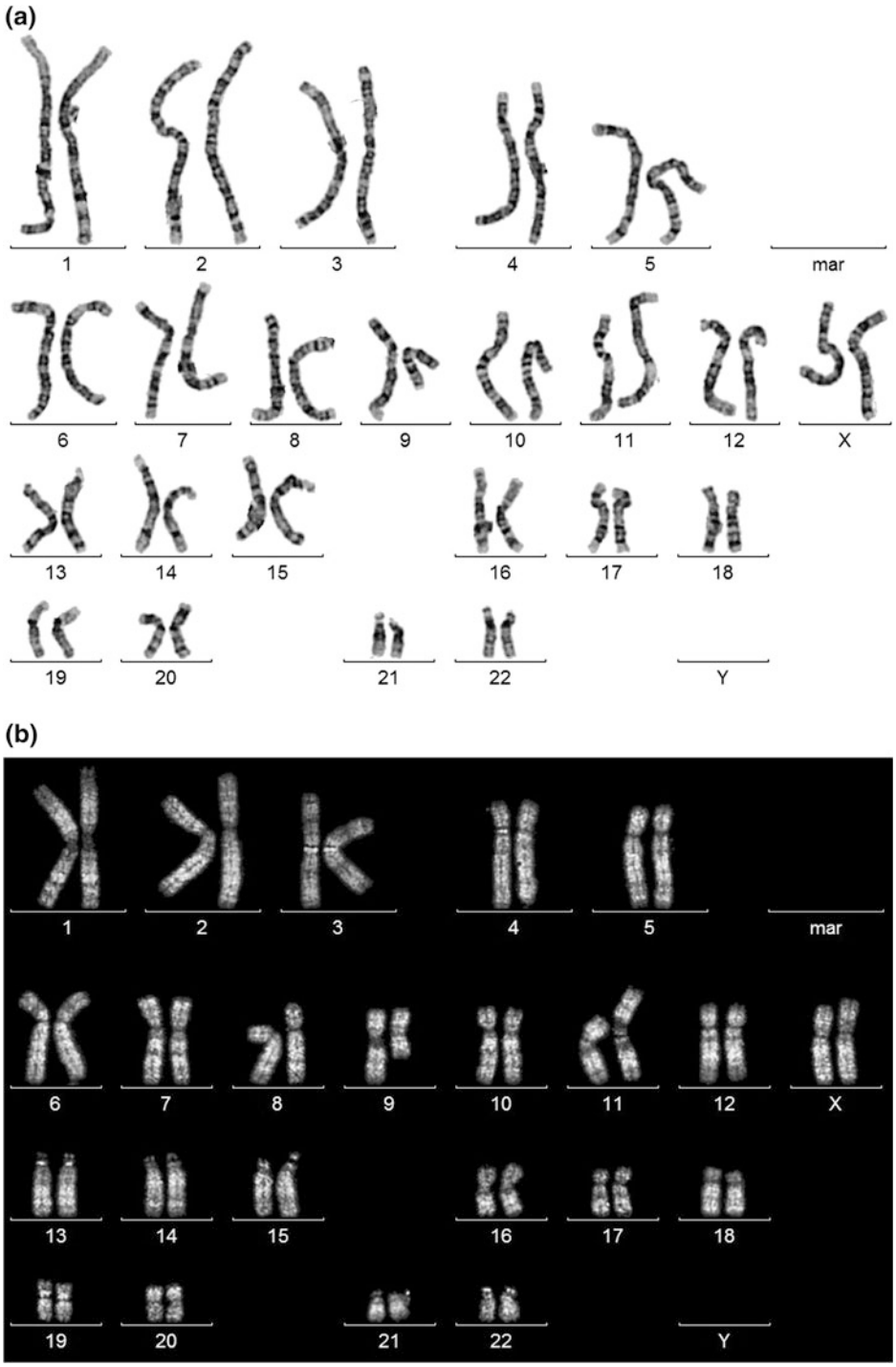

Fig. 4.74 Karyotype 46,XX,t(9;11)(q11;p11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-banding, **d** QFQ-banding, **e** GTG-banding Chromosomes from different mitoses; **d**, **e** *left* normal, *right* aberrant chromosomes 9 and 11, **f** ideograms of normal and aberrant chromosomes 9 and 11, balanced translocation

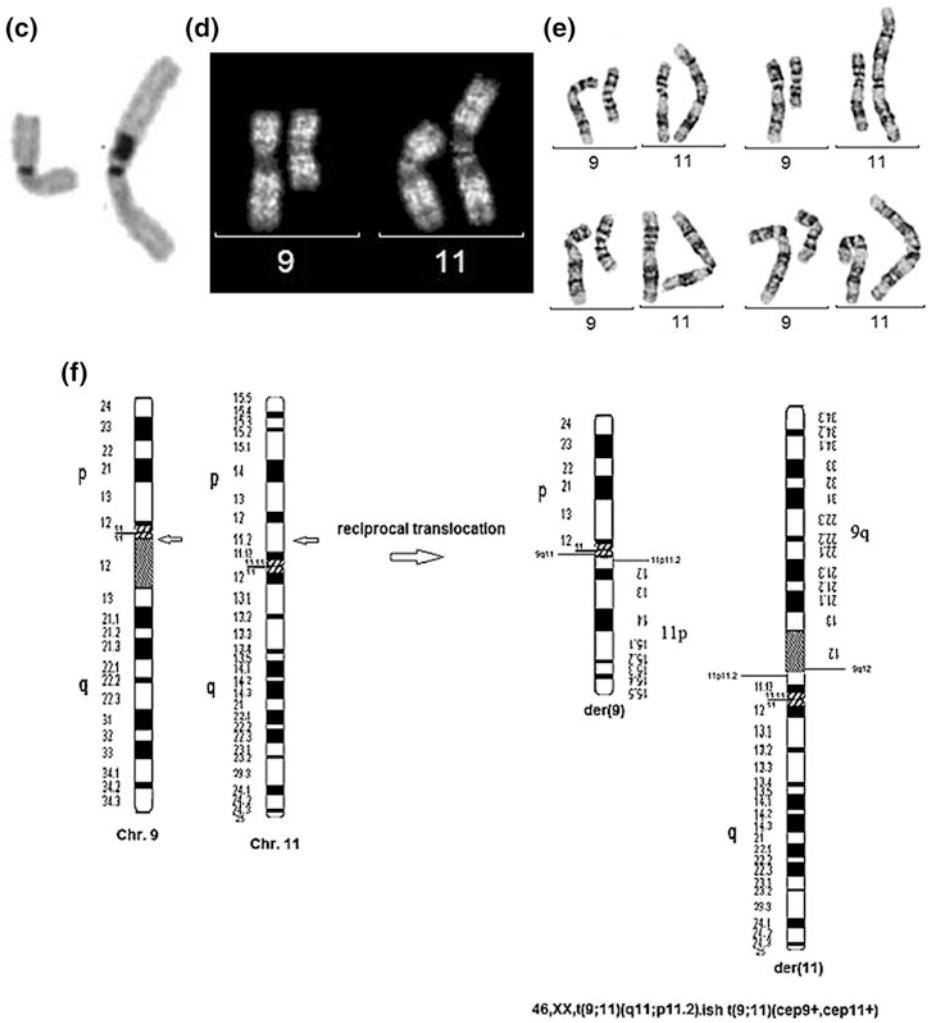

Fig. 4.74 (continued)

Case 4: Karyotype: 46,XY,der(9),t(9;12)(p24.3;q24.13), arr 12q24.13q24.33(114,023,119-133,773,499)x3 de novo

Indication for chromosome analysis: Developmental retardation, dysmorphic features.

Morphology:

One chromosome 9 is elongated in the distal region of the short arm by about 10% of its total length. It can be recognised by the altered banding pattern and the more metacentric structure.
Cave:

After analyses of normal parental karyotypes this unbalanced translocation can only be identified by microarray (Fig. 4.75).

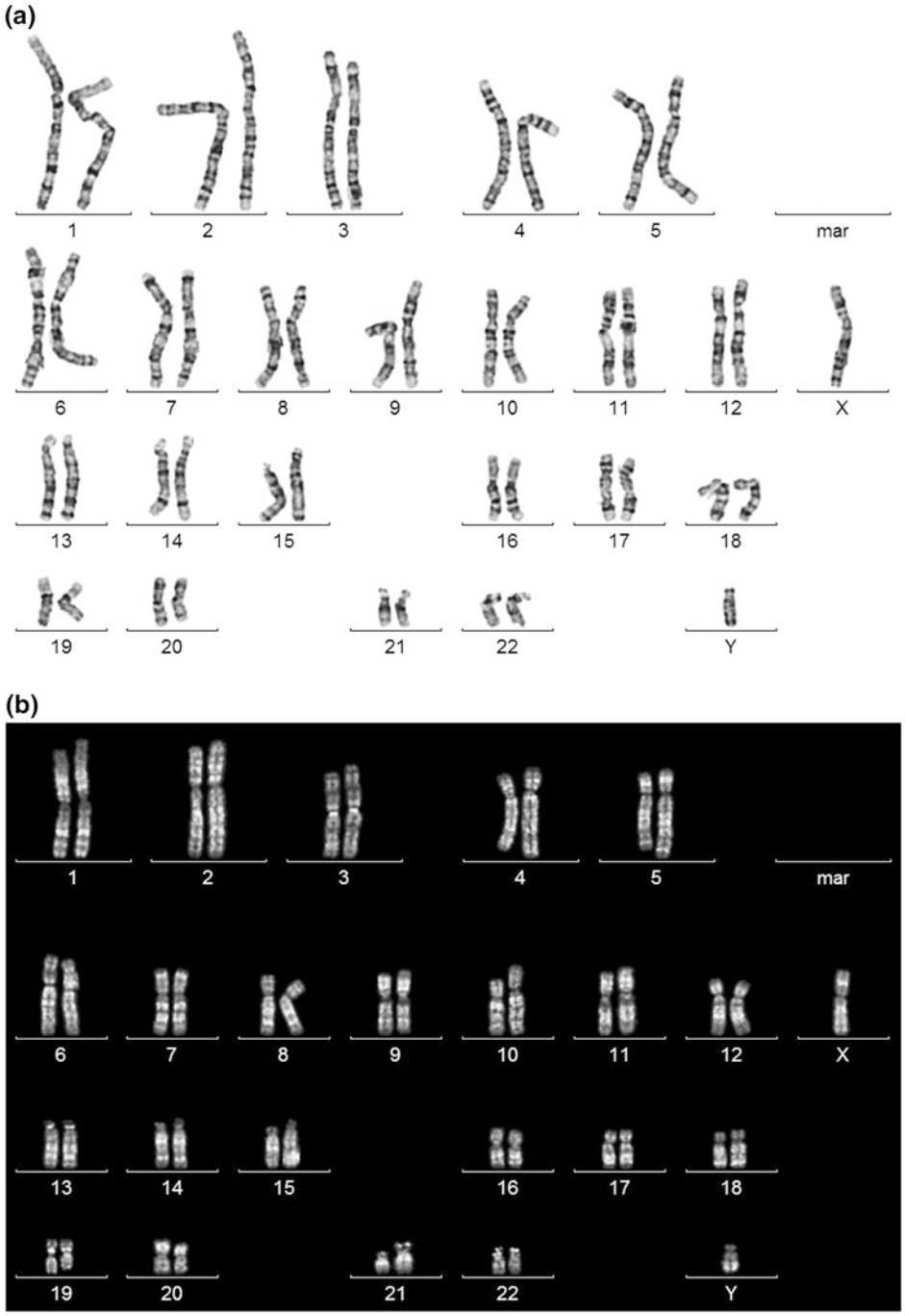

Fig. 4.75 Karyotype 46,XY,der(9),t(9;12)(p24.3;q24.13). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding chromosomes from different mitoses, *left* normal, *right* aberrant chromosome 9, **f** ideograms from normal 9 and 12 and aberrant chromosome der(9), unbalanced translocation

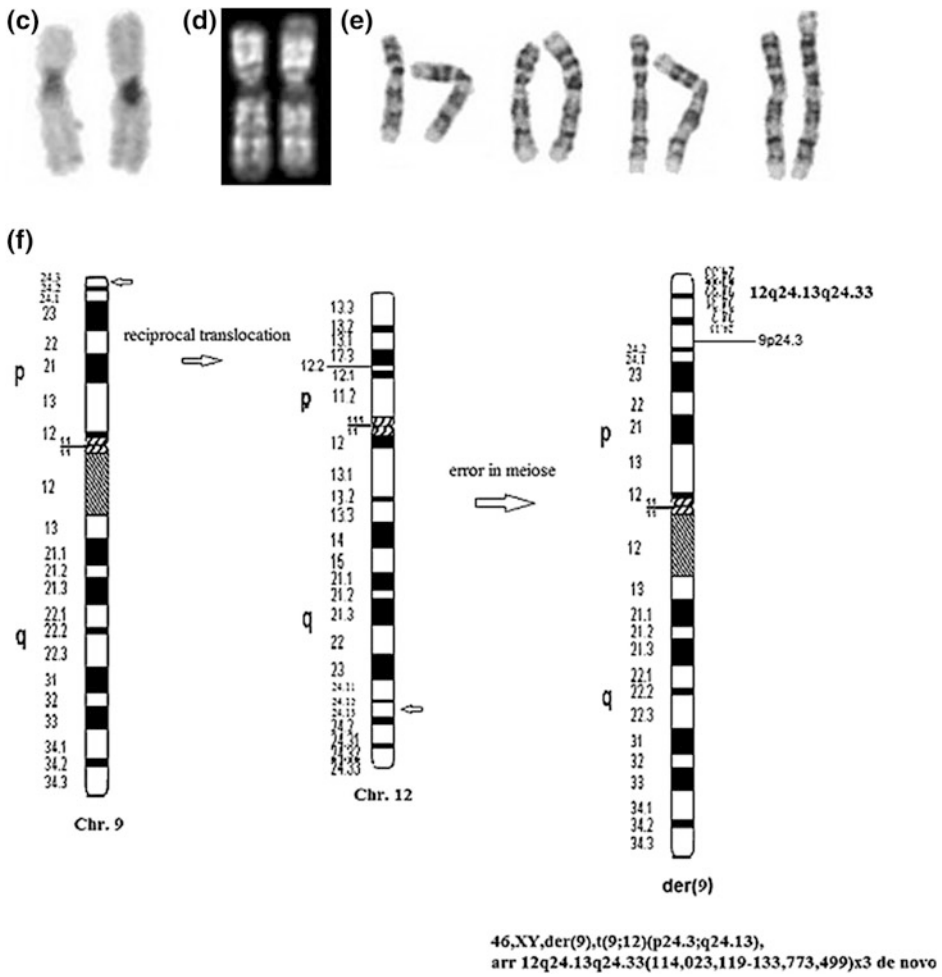

Fig. 4.75 (continued)

Case 5: Karyotype: 46,XX,t(11;22)(q23.3;q11.2)
Indication for chromosome analysis: Abortions.

Morphology:

The terminal regions of the 2 translocation chromosomes have been exchanged leading to an altered banding pattern in this regions and the size of them has changed.

Cave:

This is the most frequent reciprocal translocation in humans. The unbalanced translocation usually leads to abortion. But the derivative chromosome 22 can be malsegregated in meiosis thus occurring as supernumerary marker chromosome in the descendant. This aberration is comparable with life and presents with characteristic clinical picture (Emanuel syndrome).

Besides, in single carriers of the balanced translocation the breakpoint in chromosome 11 disrupts a gene leading to the monogenic defect of acute intermittent porphyria (AIP) (Fig. 4.76).

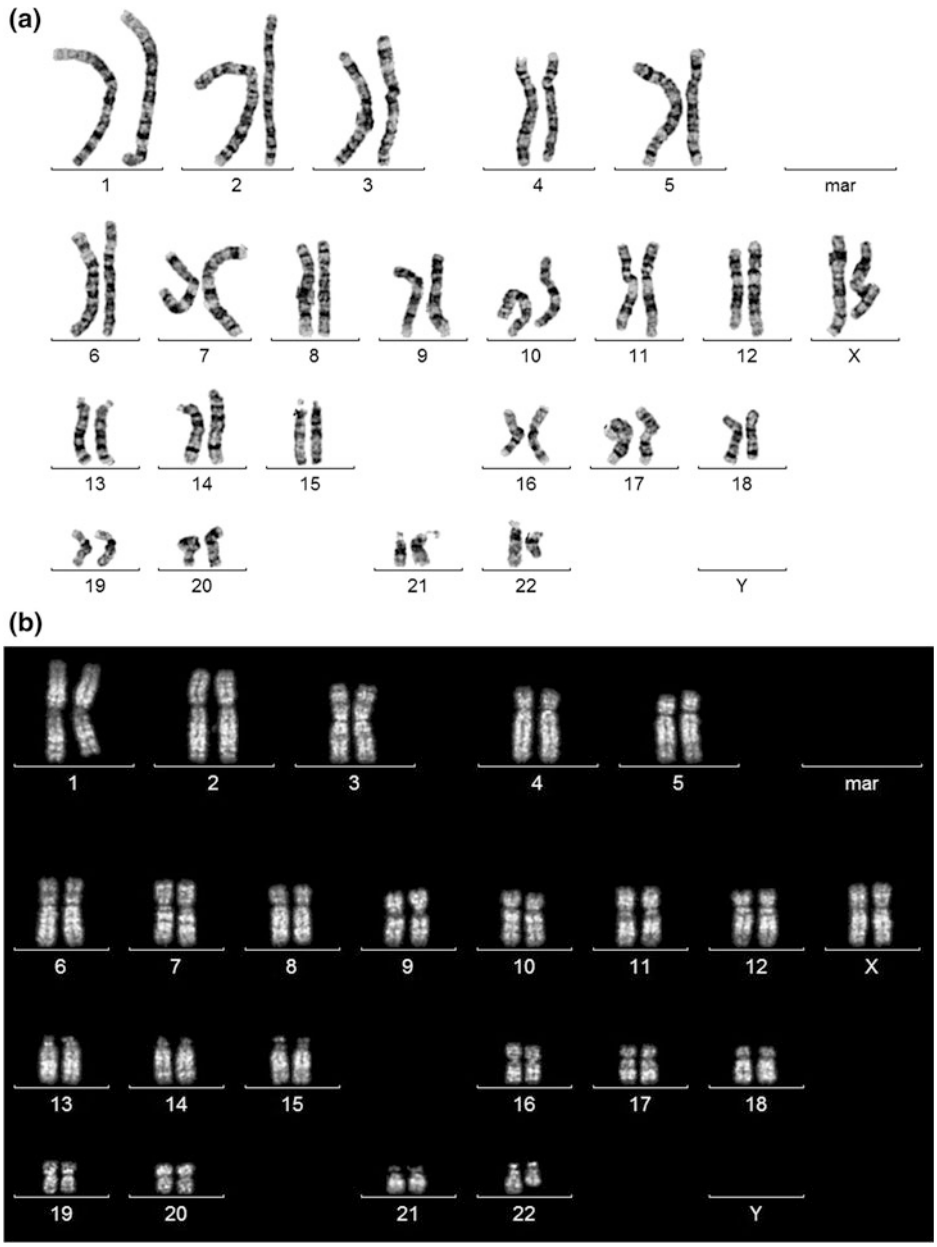

Fig. 4.76 Karyotype 46,XX,t(11;22)(q23.3;q11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** QFQ-banding, **d** GTG-banding Chromosomes from different mitoses; *left* normal, *right* aberrant chromosomes 11 and 22, **e** ideograms of normal and aberrant chromosomes 11 and 22, balanced translocation

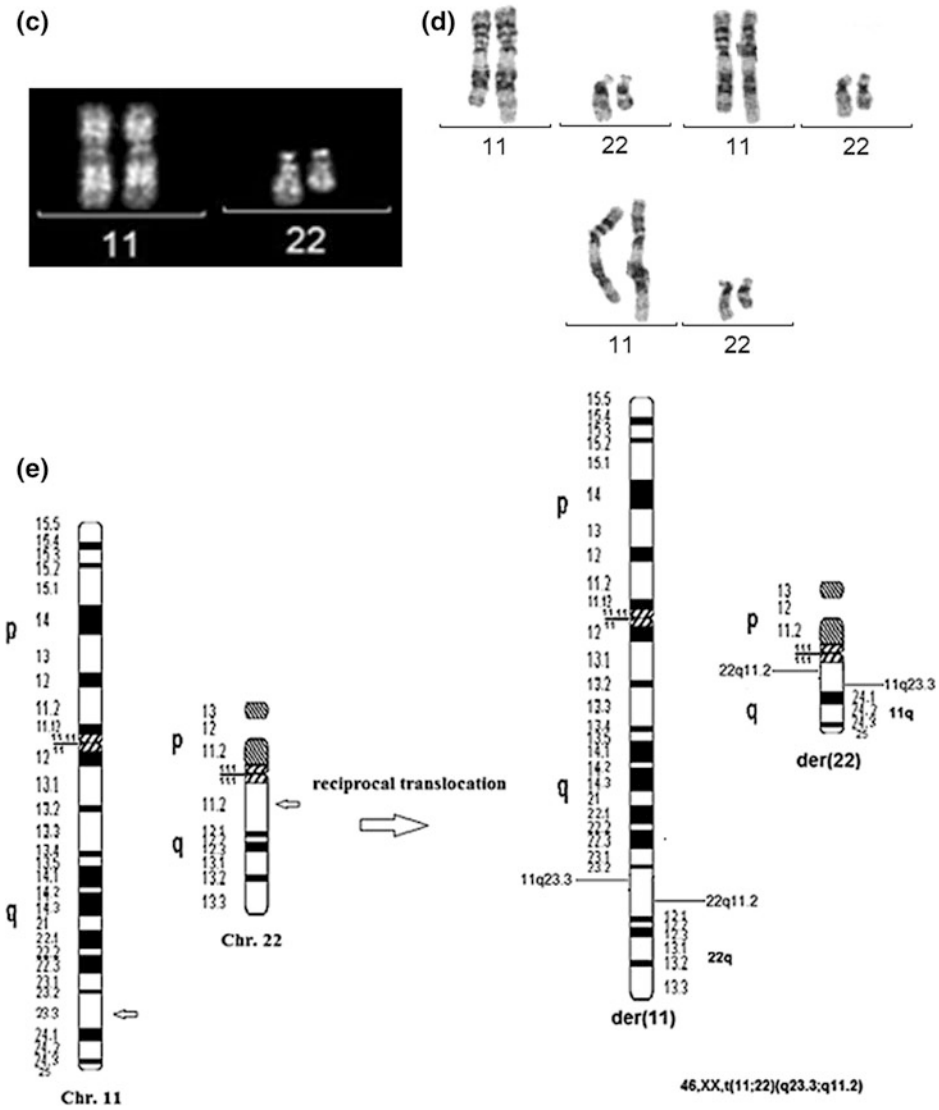

Fig. 4.76 (continued)

Case 6: Karyotype: 46,XX,t(12;18)(q10;p11.2)
Indication for chromosome analysis: Investigation of polar body is planned.

Morphology:

In chromosome 12 the centromere region is splitted, thus the larger translocation chromosome has become dicentric and its remains are almost undetectable (see C-banding). Both translocation chromosomes changed size and centromeric index compared to their normal homologues.

Cave:

In spite of the centromere splitting in chromosome 12 and a dicentric derivate the translocation chromosomes proved to be stable in transmission (Fig. 4.77).

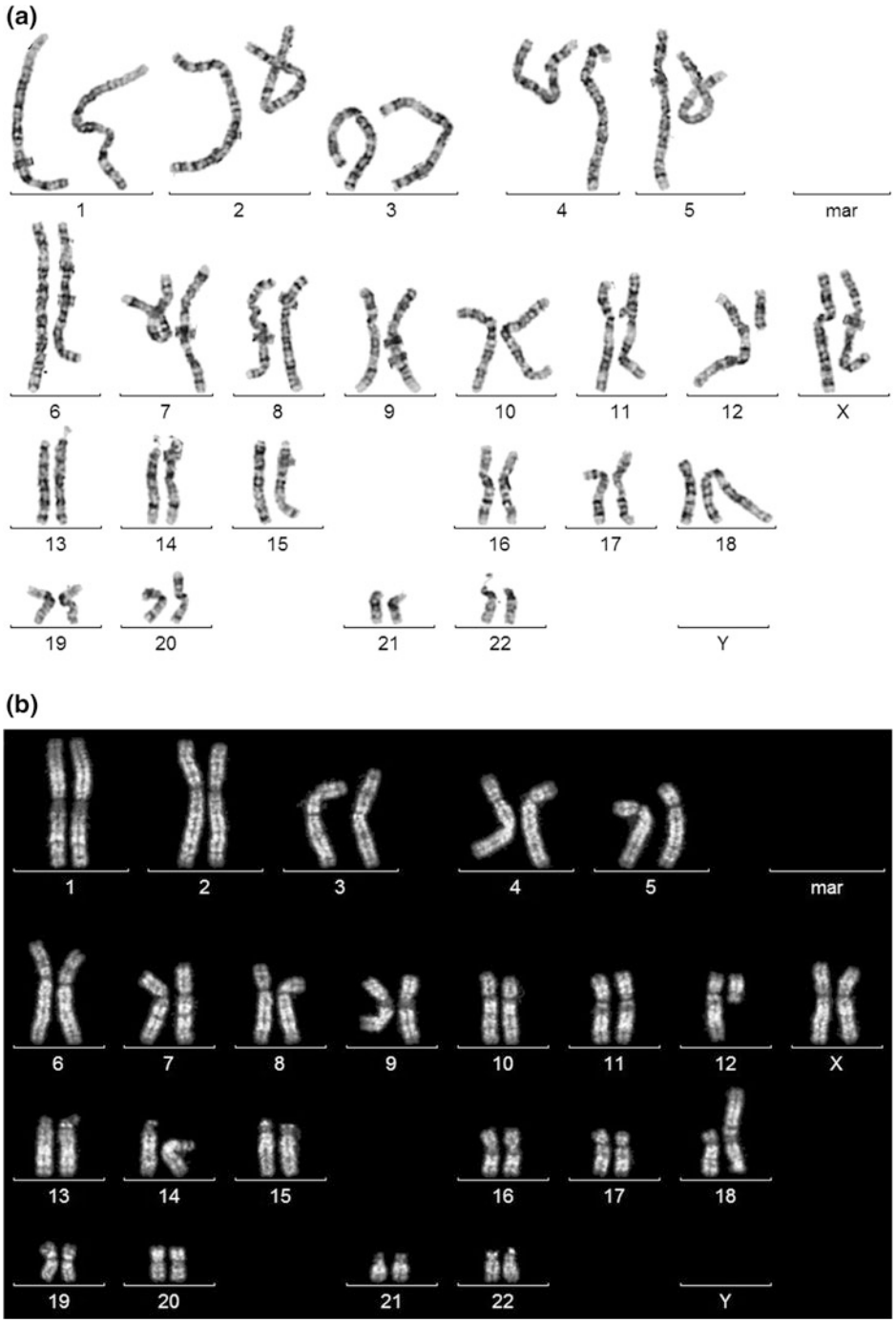

Fig. 4.77 Karyotype 46,XX,t(12;18)(q10;p11.2). **a** GTG-, **b** QFQ-banding, 850 and 400 bands per genome, **c** CBG-banding, **d** QFQ-banding, **e** GTG-banding Chromosomes from different mitoses; **d**, **e** *left* normal, *right* aberrant chromosomes 12 and 18

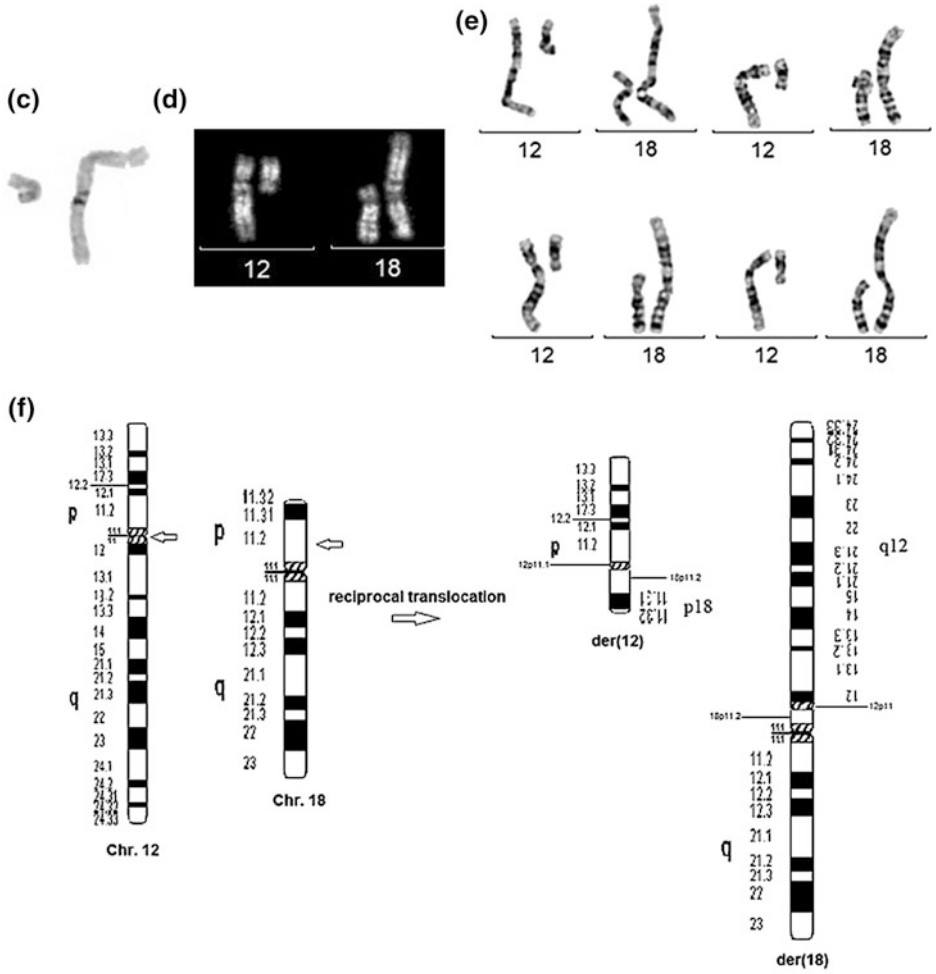

Fig. 4.77 (continued)

Case 7: Karyotype: 45,XY,der(18),t(18;22)(p11.32;q11.2), -22

Indication for chromosome analysis: Mental retardation, congenital heart defect.

Morphology:

The karyotype of the patient shows 45 chromosomes with one chromosome 22 missing. The long arms of it have been translocated on the proximal short arm region of chromosome 18. Thus the abnormal chromosome 18 is easy to identify but for exact breakpoint identification a banding resolution of at least 700 bands per genome is recommended.

Cave:

Before genetic counseling the chromosomes of the parents should be investigated. The clinical picture is caused by deletion 18p (de Grouchy syndrome I) and deletion 22q11.2 (de George syndrome) (Fig. 4.78).

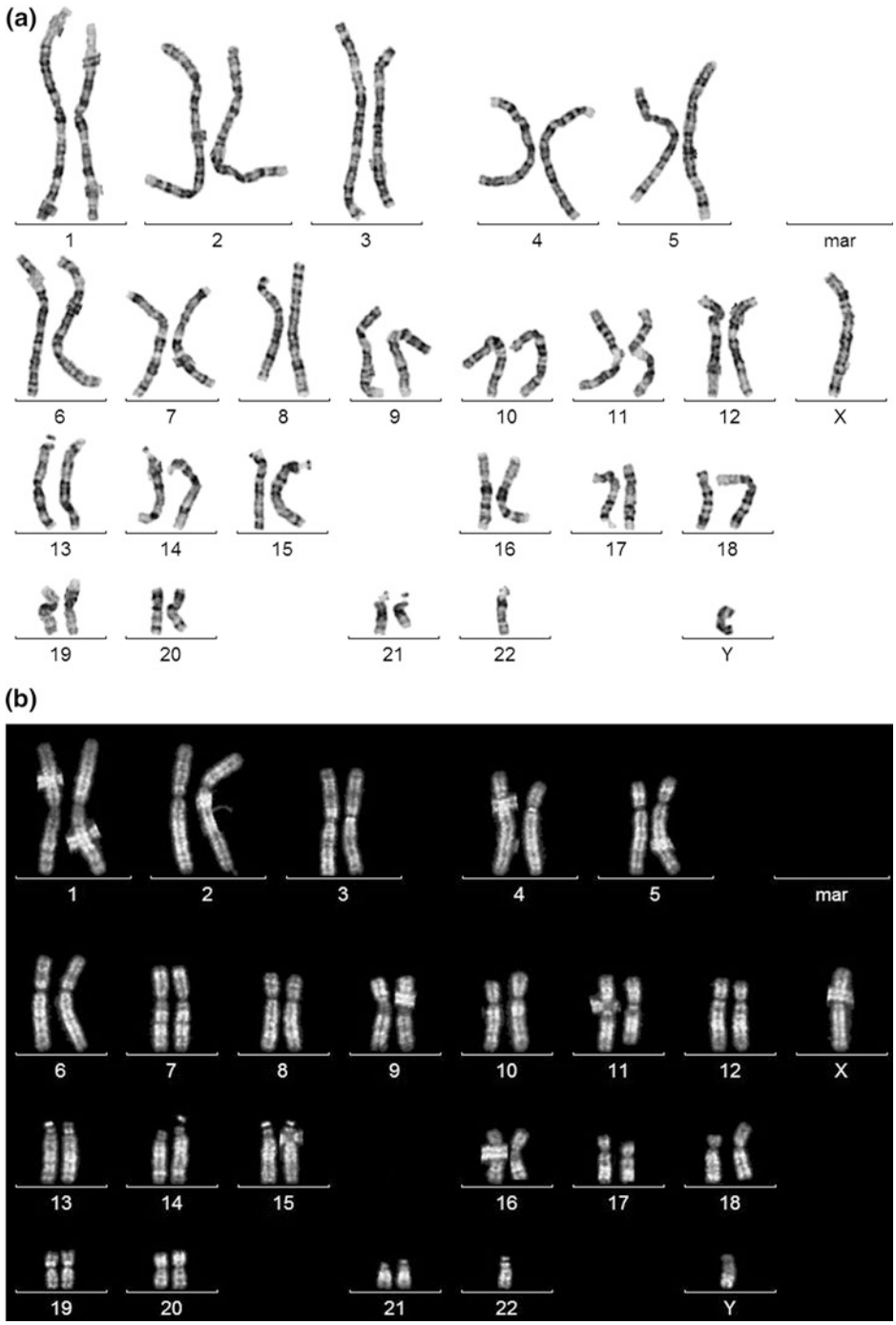

Fig. 4.78 Karyotype 46,XY,t(11;22)(q23.3q11.2). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** normal chromosomes 22 in QFQ- and GTG-banding, **d** QFQ-, **e** GTG-banding, **d**, **e** chromosomes from different mitoses, *left* normal, *right* aberrant chromosome 18, **f** ideograms from normal chromosomes 18 and 22 from the translocation product, unbalanced translocation 18/22

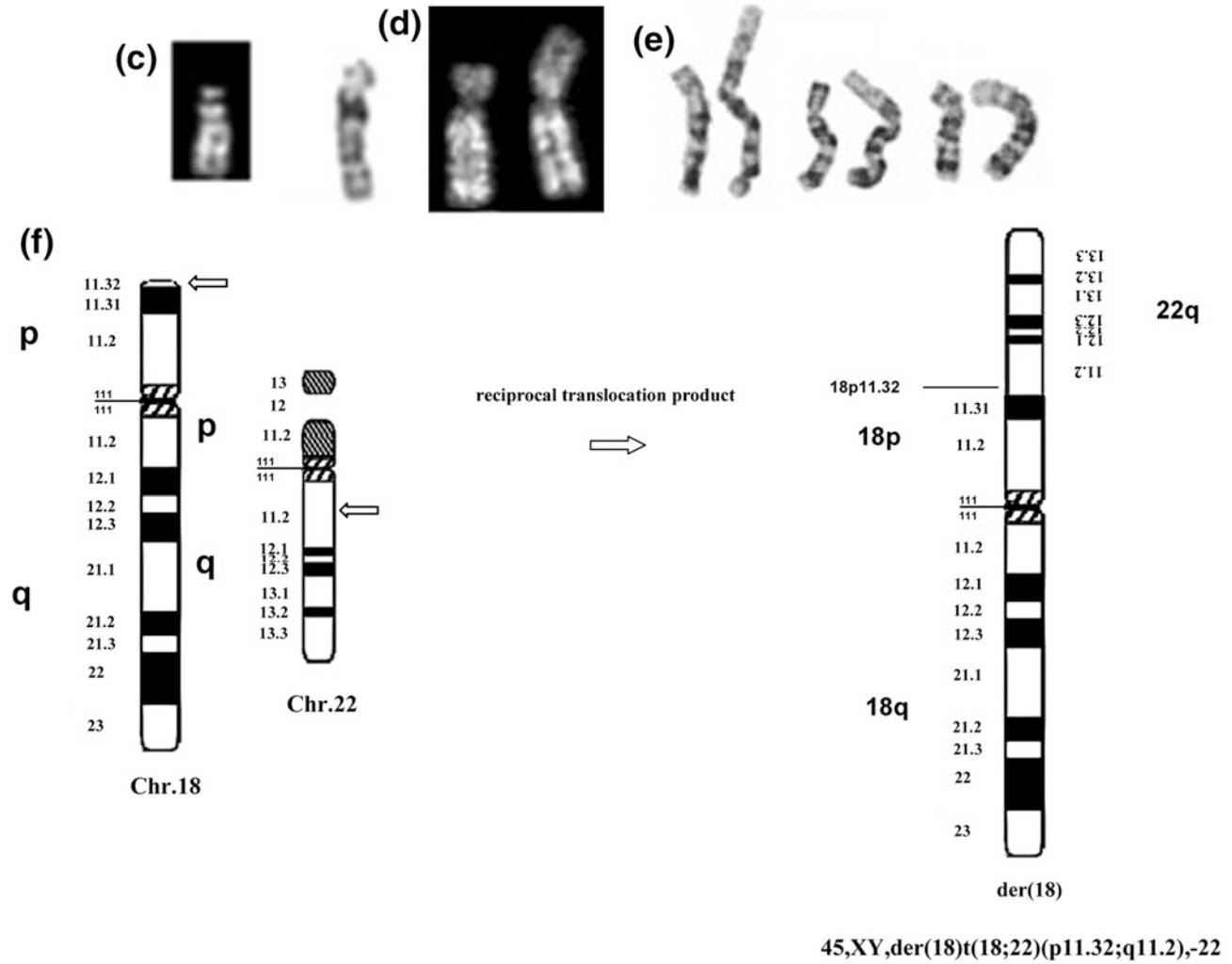

Fig. 4.78 (continued)

Case 8: Karyotype: 46,X,t(X;6)(q26.1;p25.1)
Indication for chromosome analysis: Infertility

Morphology:

The regions exchanged are very small (about 4 and 3% of the total chromosome length. Thus their identification requires a high banding resolution of more than 700 bands per genome.

Cave:

An unbalanced karyotype has to be especially discussed in a male carrier because of his X-chromosome hemizygosity (Fig. 4.79).

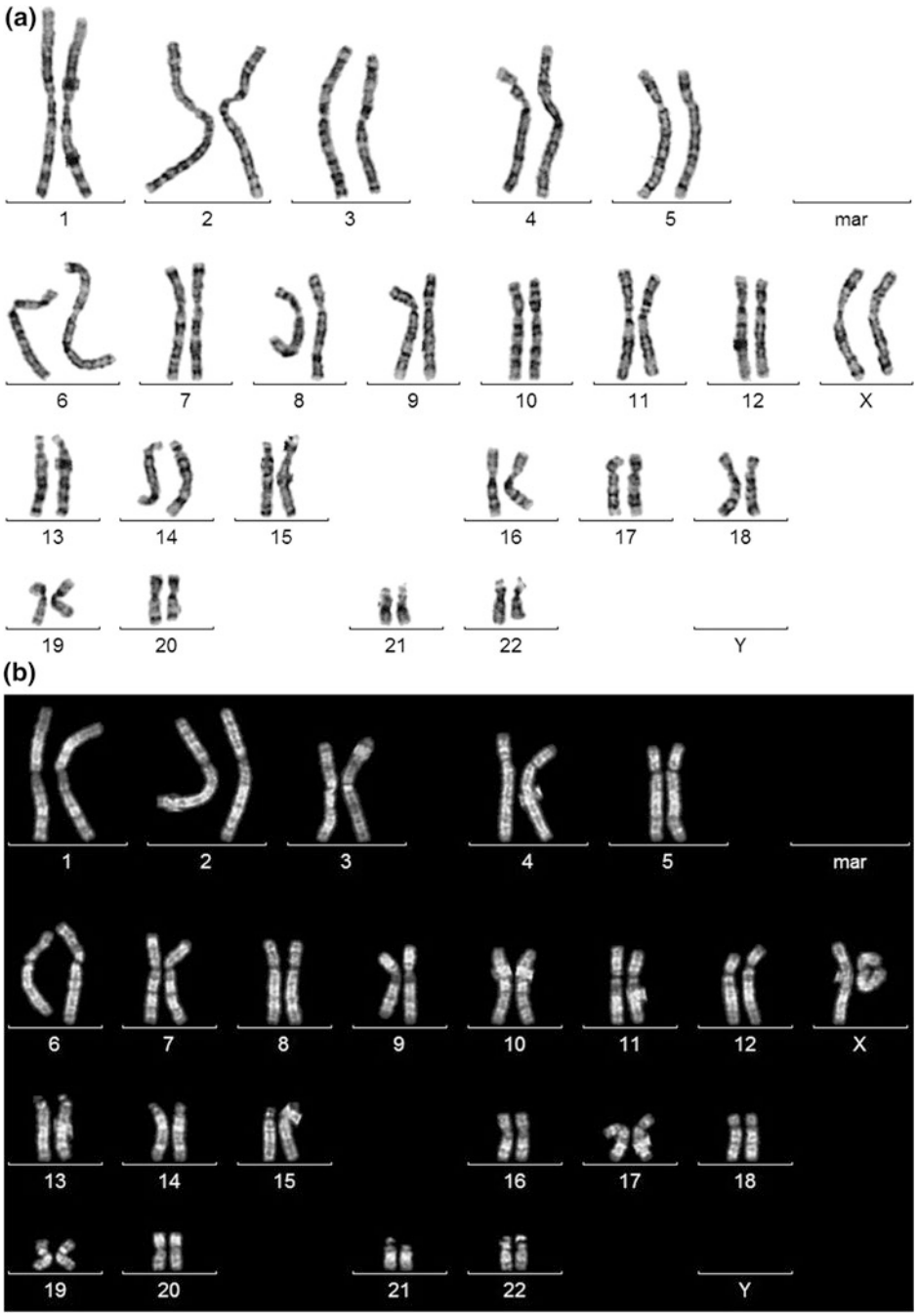

Fig. 4.79 Karyotype 46,X,t(X;6)(q26.1;p25.1). **a** GTG-, **b** QFQ-banding, both 550 bands per genome, **c** QFQ-banding, **d** GTG-banding Chromosomes from different mitoses; *left* normal, *right* aberrant chromosomes X and 6, **e** ideograms of normal and aberrant chromosomes X and 6, balanced translocation

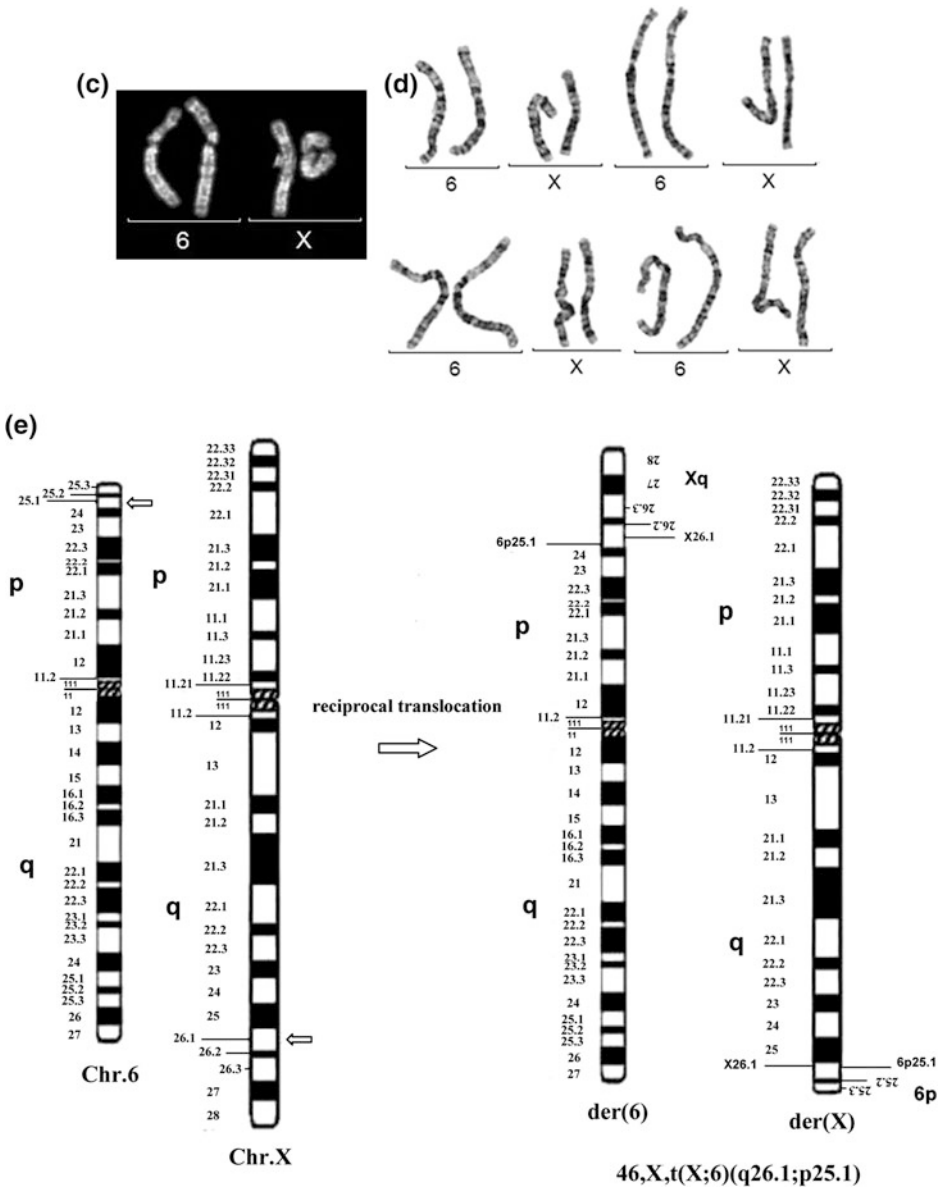

Fig. 4.79 (continued)

Case 9: Karyotype: 46,X,t(Y;5)(q11.21;p15.33)
Indication for chromosome analysis: OAT-syndrome.

Morphology:

As the distal part of the long arm of the Y-chromosome has been exchanged with the distal band of 5p beside GTG banding, QFQ and CBG must be applied. The banding resolution should be at least 700 bands per genome.

Cave:

As to our experience with Y/autosome translocations pairing abnormalities in meiosis are frequently leading to meiotic arrest at the end of the prophase (Fig. 4.80).

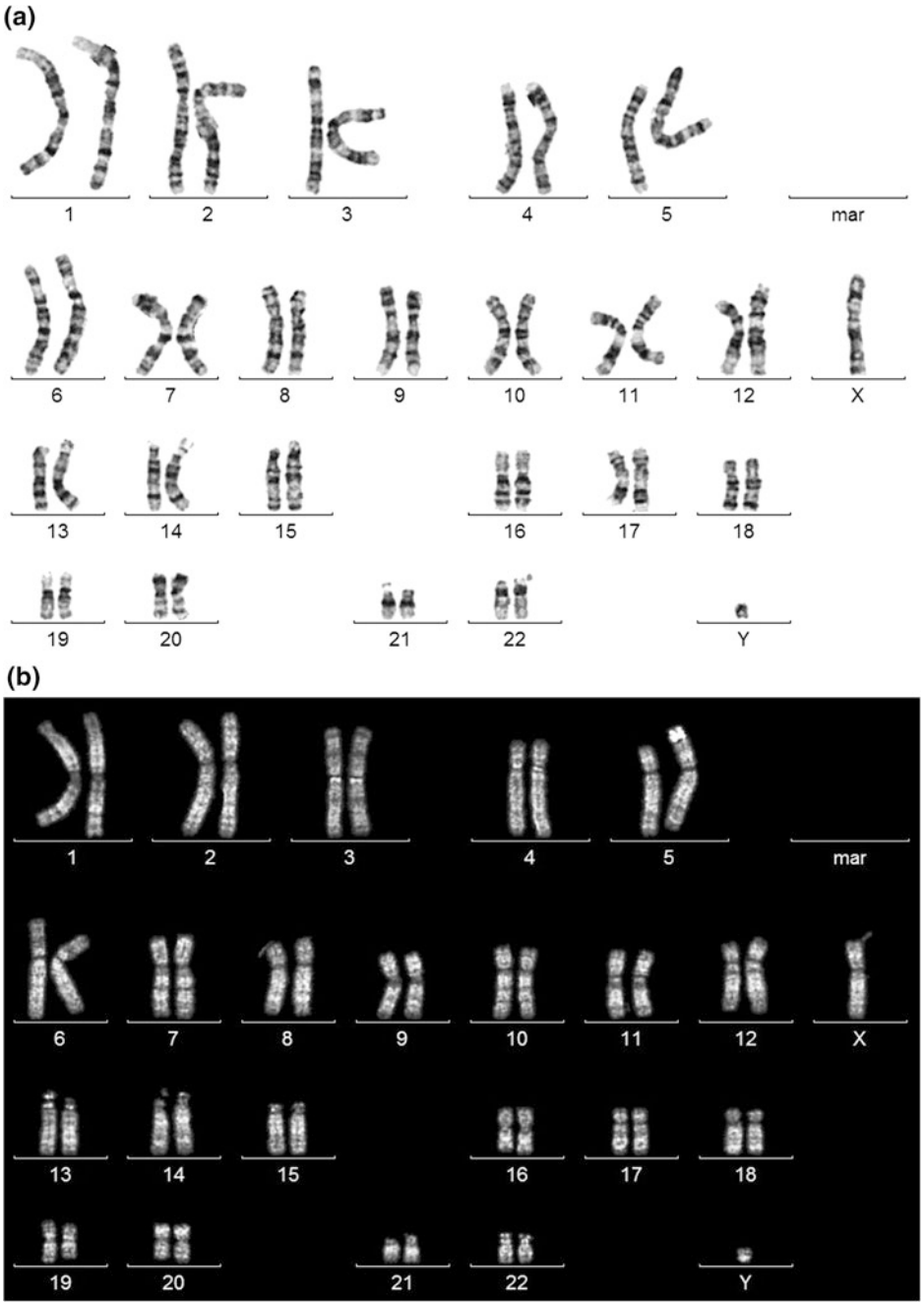

Fig. 4.80 Karyotype 46,X,t(Y;5)(q11.21;p15.33). **a** GTG-, **b** QFQ-banding, both 550 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, here 1 metaphase with 2 Y-derivates. Chromosomes from different mitoses; **d**, **e** *left* normal chromosomes, *right* the 2 derivates; **d** on the *right* normal Y-chromosome, **f** ideograms from normal and aberrant chromosomes Y and 5, balanced translocation

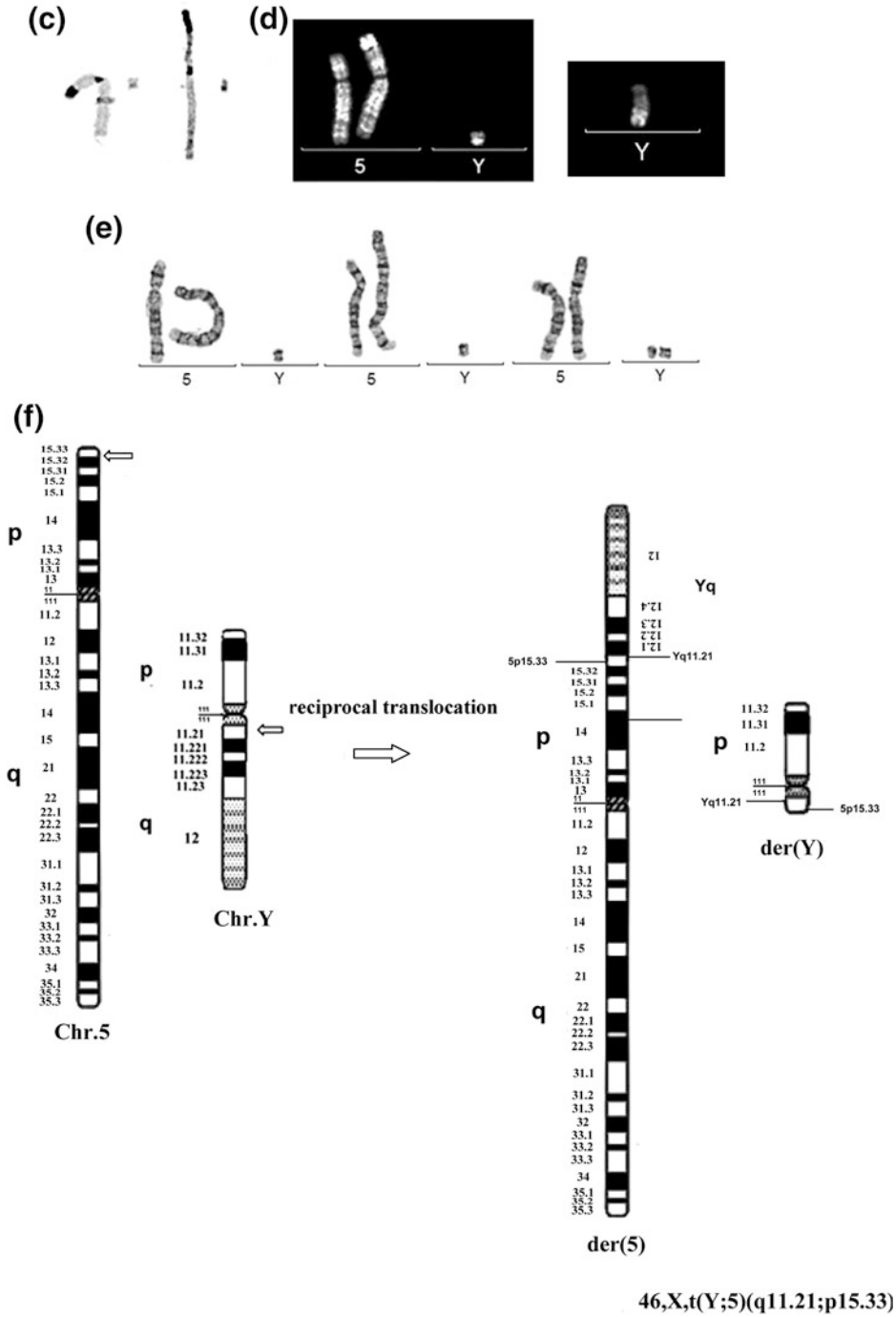

Fig. 4.80 (continued)

Summary

A total of 9 different reciprocal translocation is presented in detail. Of these 7 rearrangements are between 2 autosomes, 1 is an X/autosome and 1 a Y/autosome translocation.

In the family with reciprocal translocation 2/18 12 persons from 3 generations could be investigated. The carriers of an unbalanced translocation showed both possible forms of a partial duplication and partial deletion in equal frequency (see pedigree). Male and female carriers of the translocation were equal often observed. The amount of abortions was—according to informations from the family—not increased. Unexpected was the high frequency of unbalanced translocations, inherited paternally (4 out of 8 pregnancies), which according to empiric inquiries is estimated to be about 10%. Thus this familial case makes it obvious that in reciprocal translocations the genetic risk factor can be estimated more precise after detailed family investigations.

The case of an unbalanced translocation 18/22 by loss of the smaller translocation chromosome is a typical example for an additional risk factor in reciprocal translocations by aneuploidisation. This has to be taken into account when one of the translocation chromosomes is small, so that the common regions for pairing with the homologues in prophase of meiosis I are reduced in size.

The unbalanced translocation 9/12 presented here is a good example for the requirement of additional investigations by microarray to get the precise analysis of the karyotype in cases when the second translocation chromosome cannot be identified by banding techniques in an unbalanced rearrangement.

The X/6 translocation and the Y/15 translocation were both identified in healthy carriers with infertility.

The spectrum of reciprocal translocations presented here illustrates their different mode of ascertainment and risk of estimation.

Robertsonian Translocations

1 45,XX,dic rob(13;14)(p11.2;p11.1)

Case 1: Karyotype: 45,XX,dic rob(13;14)(p11.2;p11.1)

Indication for chromosome analysis: Multiple abortions, relative with Down syndrome.

Morphology:

The total chromosome number is 45. A fusion has occurred between the proximal short arm regions of chromosome 13 (breakpoint p11.2) and 14 (breakpoint p11.1). The fusion product is dicentric, always with inactivation of the chromosome 13 centromere. The region in between the 2 centromeres can be easily characterised by C-banding or QFQ-banding (brilliant fluorescence). The distal part of 13p and the whole short arm of chromosome 14 got lost, which is of no relevance for the carrier, as they are composed of constitutive heterochromatin.

Cave:

When the carrier is asking for genetic counseling beside structural and numerical chromosome aberrations functional abnormalities by partial or complete UPD 14 have to be discussed (Fig. 4.81).

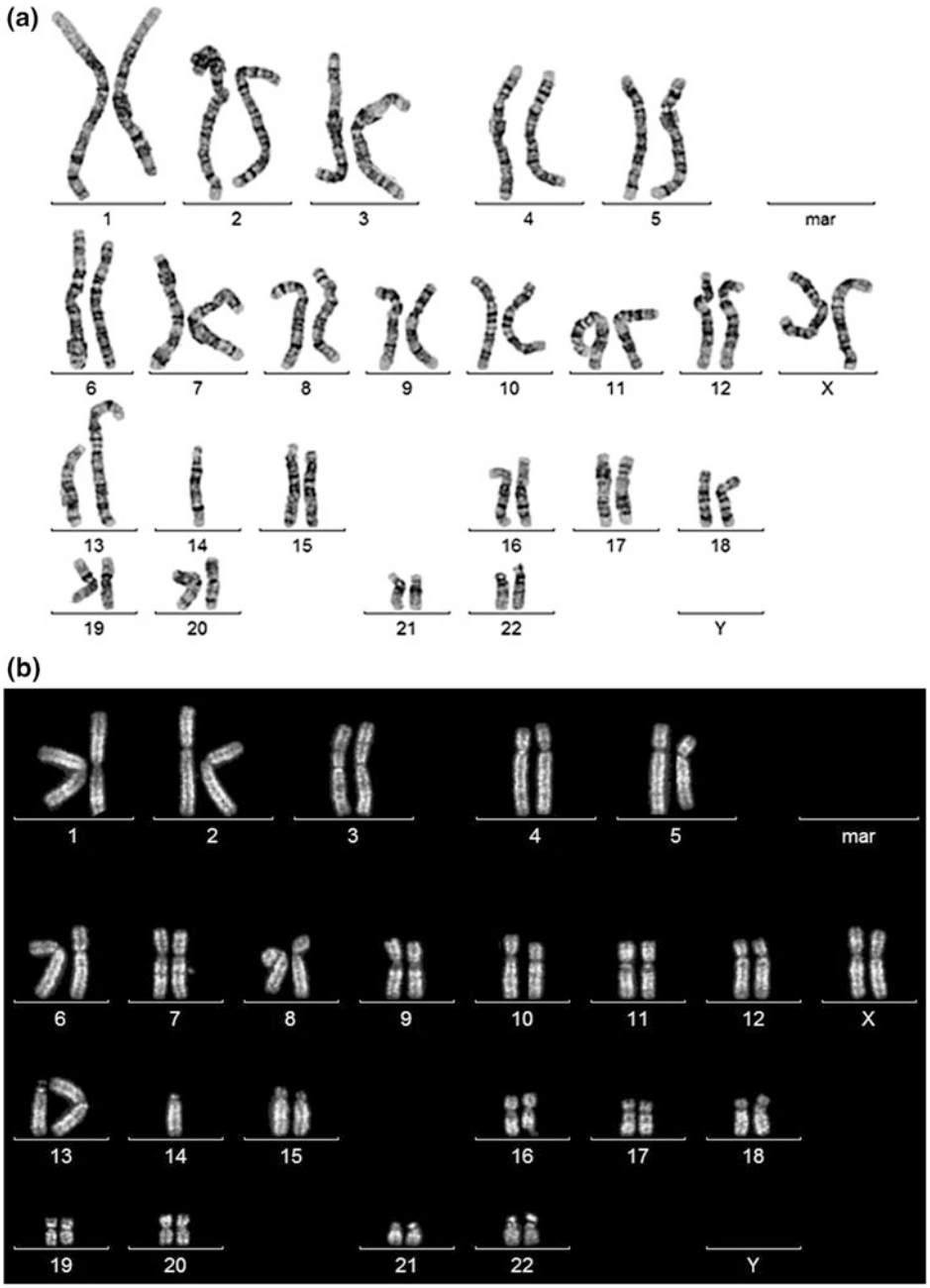

Fig. 4.81 Karyotype 45,XX,dic,rob(13;14)(p11.2;p11.1). **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** CBG-banding, **d** QFQ-banding, **e** GTG-banding, chromosomes from different mitoses; **d**, **e** left and *right* normal chromosomes 13 and 14, in between: fusion product, **f** ideograms of normal chromosomes 13 and 14 and fusion product, balanced rearrangement

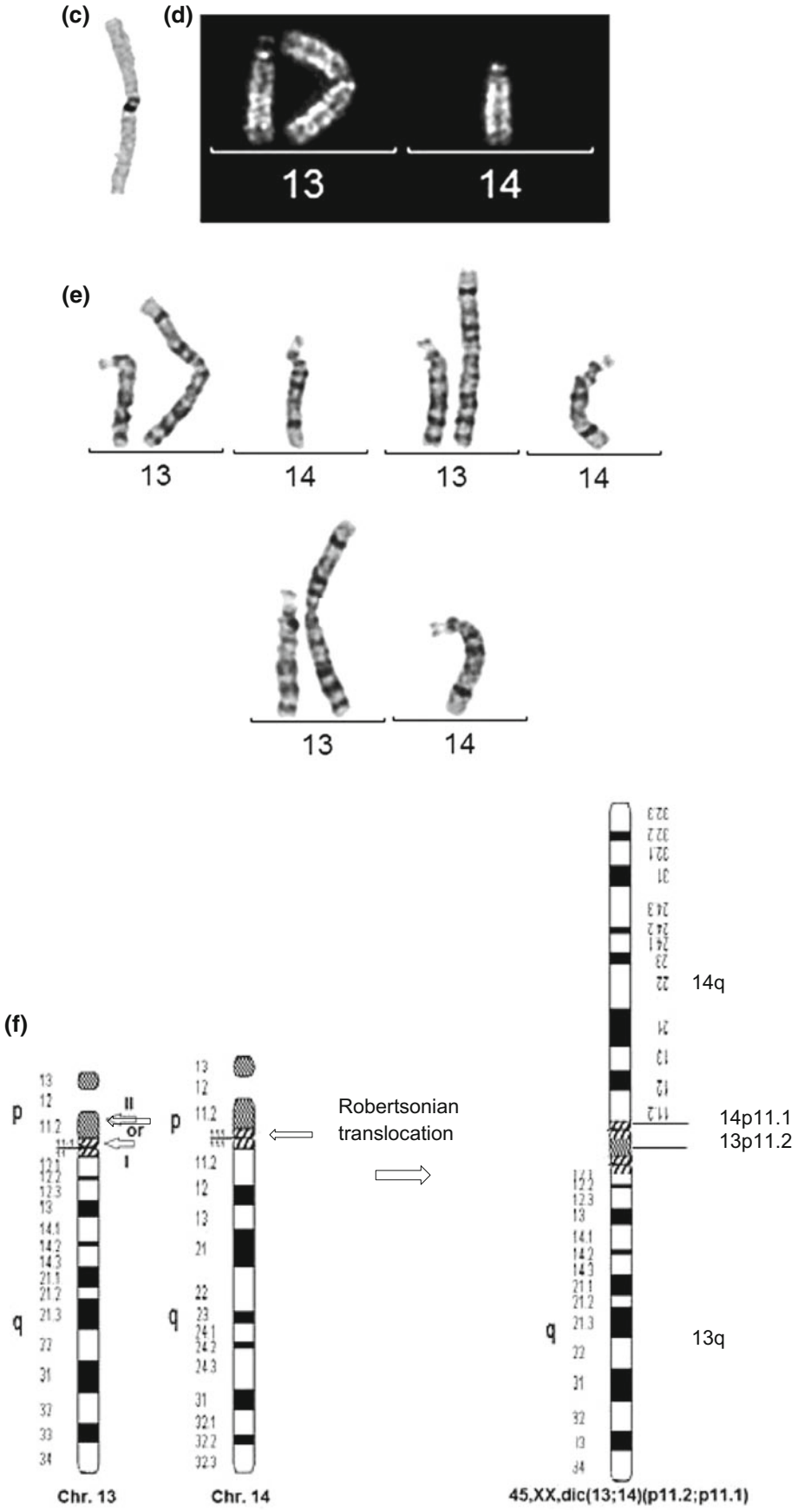

Fig. 4.81 (continued)

Summary

As an example for this special but frequent type of translocation the centric fusion 13/14 is described in detail. Here, the translocation chromosome is practically always dicentric, caused by homologous but inverted heterochromatic regions in the proximal parts of the short arms in both chromosomes. The balanced carrier has 45 chromosomes as the second translocation chromosome composed of the distal short arm regions is acentric and therefore gets lost in mitosis. The genetic risk for the balanced carrier is complex: The fertility is reduced in both sexes but particularly in the males, the risk of abortion is significantly increased (cases of trisomy 13 and 14), birth of a child with translocation-trisomy 13 is less than 1%, and additionally UPD-14 and partial proximal UPD-14 have to be taken into account in offspring with balanced and normal appearing karyotype as well as the possibility of partial duplications and deletions of euchromatin by an unequal crossing over in meiosis.

In the first years of the translocation investigations in familial cases it was assumed that pairing abnormalities in meiosis can lead to malsegregation of heterologous chromosomes not involved in the translocation especially chromosome 21 and that thus the risk for the birth of a child with trisomy 21 is increased. More detailed investigations made it obvious that the reduced fertility of a carrier with 13/14 translocation is the reason for a higher amount of pregnancies in these couples in an advanced maternal age. This means that the risk for trisomy 21 in the offspring is the well-known age factor and not caused by the translocation.

4.2.2.2 Insertions

1 46,XX ins(6;5)(q13;q31.1q33.1)

Case 1: Karyotype: 46,XX ins(6;5)(q13;q31.1q33.1)

Indication for chromosome analysis: Identic isochromosome in the daughter.
Morphology:

The chromosomes involved in the balanced rearrangement are diagnosed by the altered length of the long arms of chromosome 5 and 6, and by the aberrant banding pattern. The chromosome analysis must be performed at a resolution of 550–700 bands per genome. Additional microarray investigation is indicated.

Cave:

The family investigation should be extended to all relatives which are possible insertion carriers. As the risk for an unbalanced karyotype in the offspring is high (about 30%) prenatal diagnosis including microarray should be recommended to all carriers (Fig. 4.82).

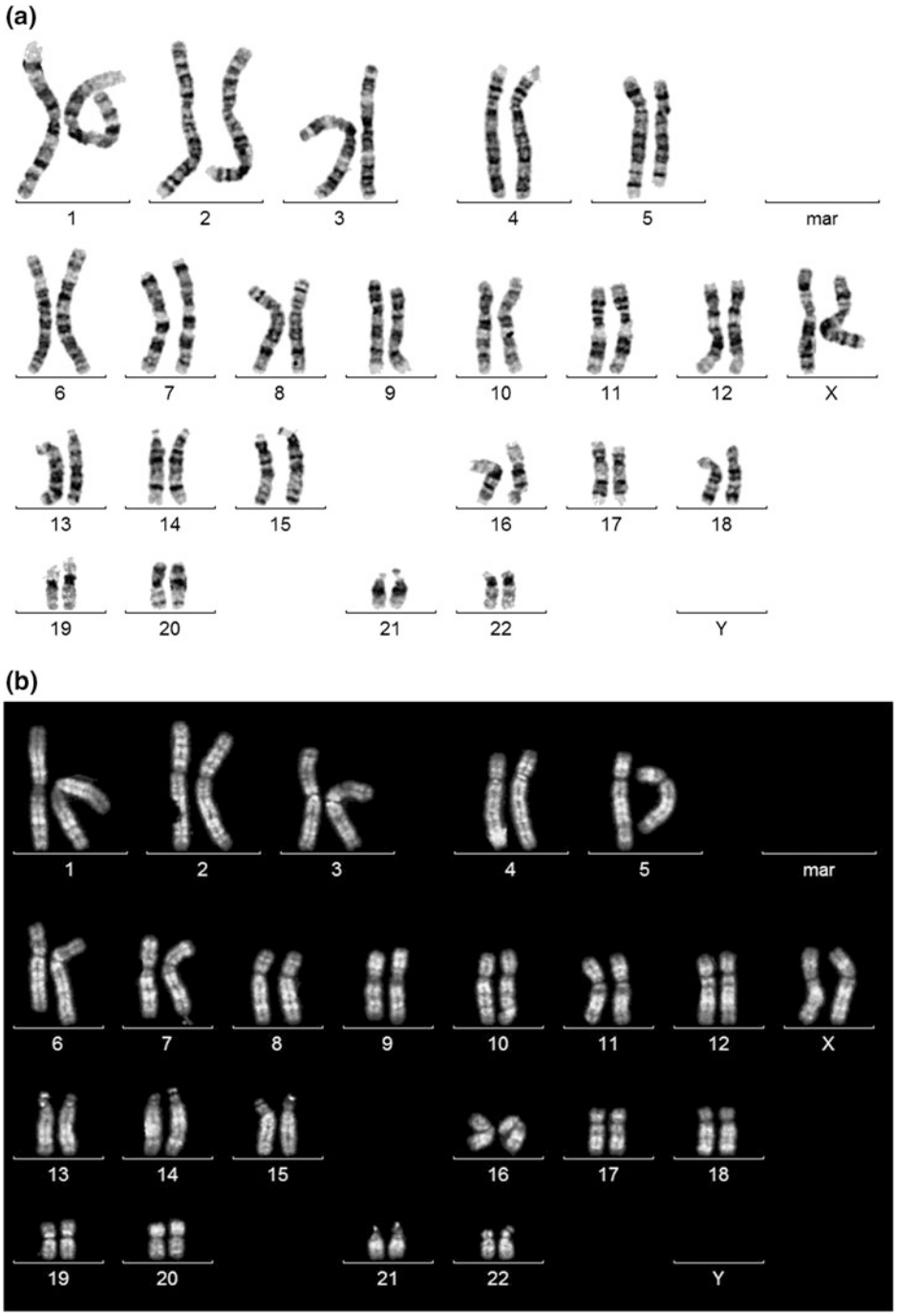

Fig. 4.82 Karyotype 46,XX,ins(6;5)(q13;q31.1q33.1). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal chromosomes 5 and 6, *right* products of rearrangement, **e** ideograms of normal chromosomes 5 and 6 and the products of rearrangement, balanced karyotype

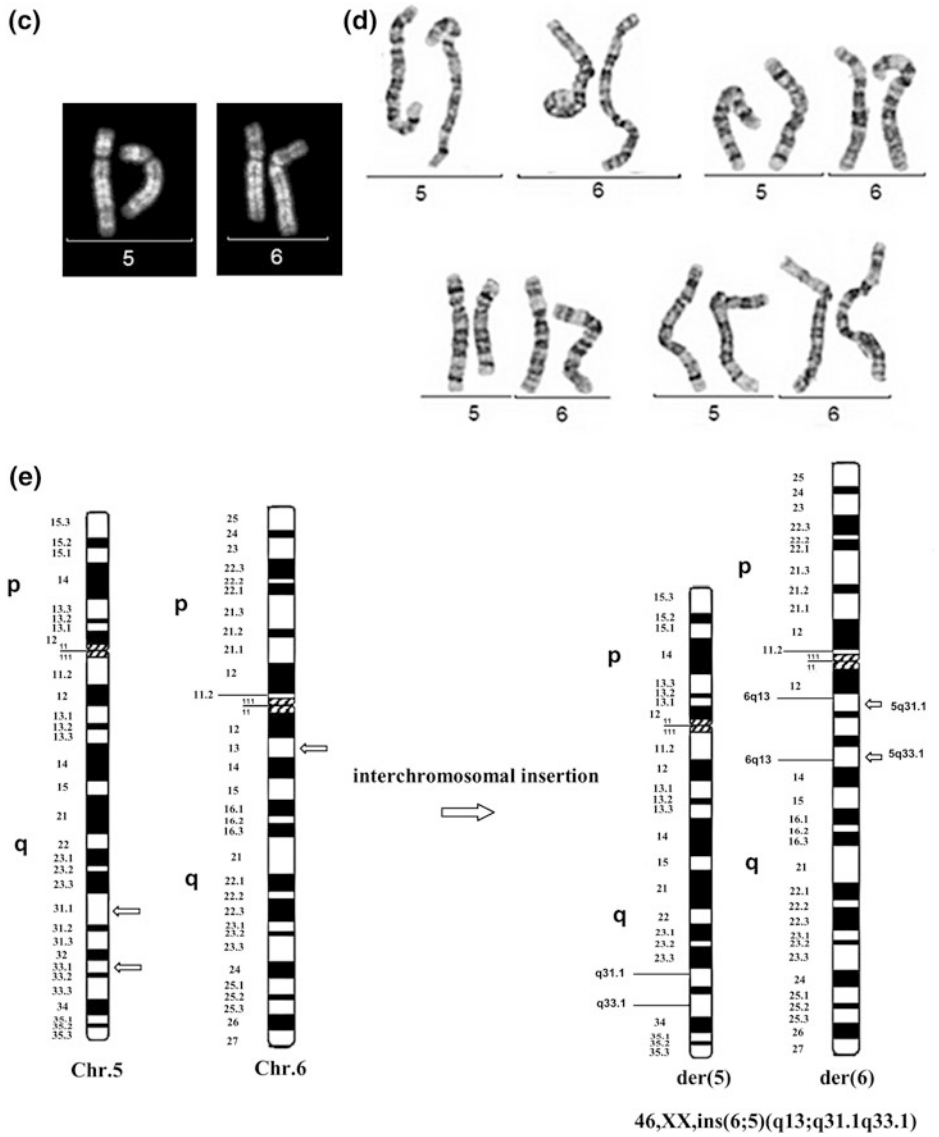

Fig. 4.82 (continued)

Summary

Different types of insertions have been characterised. The insertion can be caused by three breakpoints and the acentric fragment from a donor chromosome with two breakpoints inserted into a recipient with one breakpoint. The larger chromosomes 1–12 are more often involved than the smaller ones (13-Y). This procedure can occur between the chromatids of one chromosome, between homologous or heterologous chromosomes. The translocated segment can be euchromatic or heterochromatic in origin and it can be inserted directly or after inversion. The frequency of insertions is very low with a total amount of 1 in 80.000 newborn. The genetic risk is the same for directly inserted and for inverted segments. The risk factor for a life born child with unbalanced karyotype is low (<10%) in large inserted segments and in those which are gene rich (GC-regions) and high in AT-rich segments of small size (up to 50%). Lethality is especially high if the unbalanced karyotype has a deletion for the segment in question. Therefore a detailed analysis including relatives of the carrier is necessary in each case.

The case of a familial direct insertion 5/6 is described in detail. The genetic risk includes an unbalanced karyotype with interstitial deletion or duplication 5q31.1q33.1 and additionally submicroscopic aberrations by unequal crossing over in meiosis. The viability of the carrier of an unbalanced karyotype depends on the size and the gene content of the inserted segment.

4.2.2.3 Complex Chromosome Rearrangements (CCR)

1 46,XX,inv(2)(p11.2q13),del(18)(q22)
2 46,XY,del(5)(q14.2q22.1),t(16;20)(q24;q13.11)
3 47,XY,inv(12)(q15q24.1),+dic,der(15)(pter→q11.2::q11.2→pter)

Case 1: Karyotype: 46,XX,inv(2)(p11.2q13),del(18)(q22)
Indication for chromosome analysis: Phenotype of de Grouchy syndrome II.

Morphology:

The patient shows a complex structural aberration (CCR), involving 2 chromosomes with 3 breakpoints.

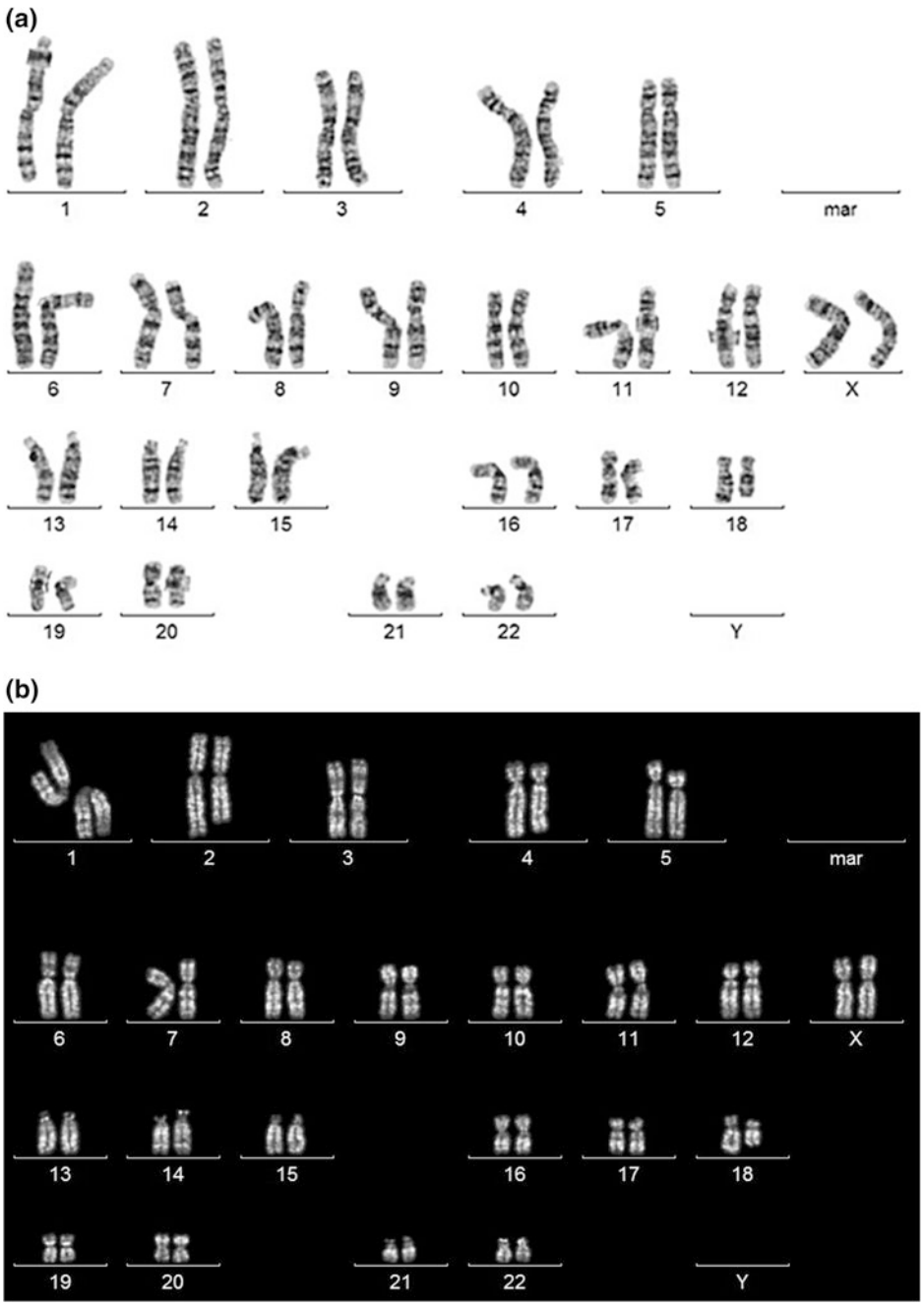

Fig. 4.83 Karyotype 46,XX,inv(2)(p11.2q13),del(18)(q22). **a** GTG- **b** QFQ-banding, 550 and 400 bands per genome, **d** QFQ-, **c**, **e** GTG-banding, chromosomes from different mitoses, *left* normal, *right* aberrant chromosomes 2 and 18, **f** ideograms of normal and aberrant chromosomes 2 and 18; 2: balanced, 18: unbalanced rearrangement

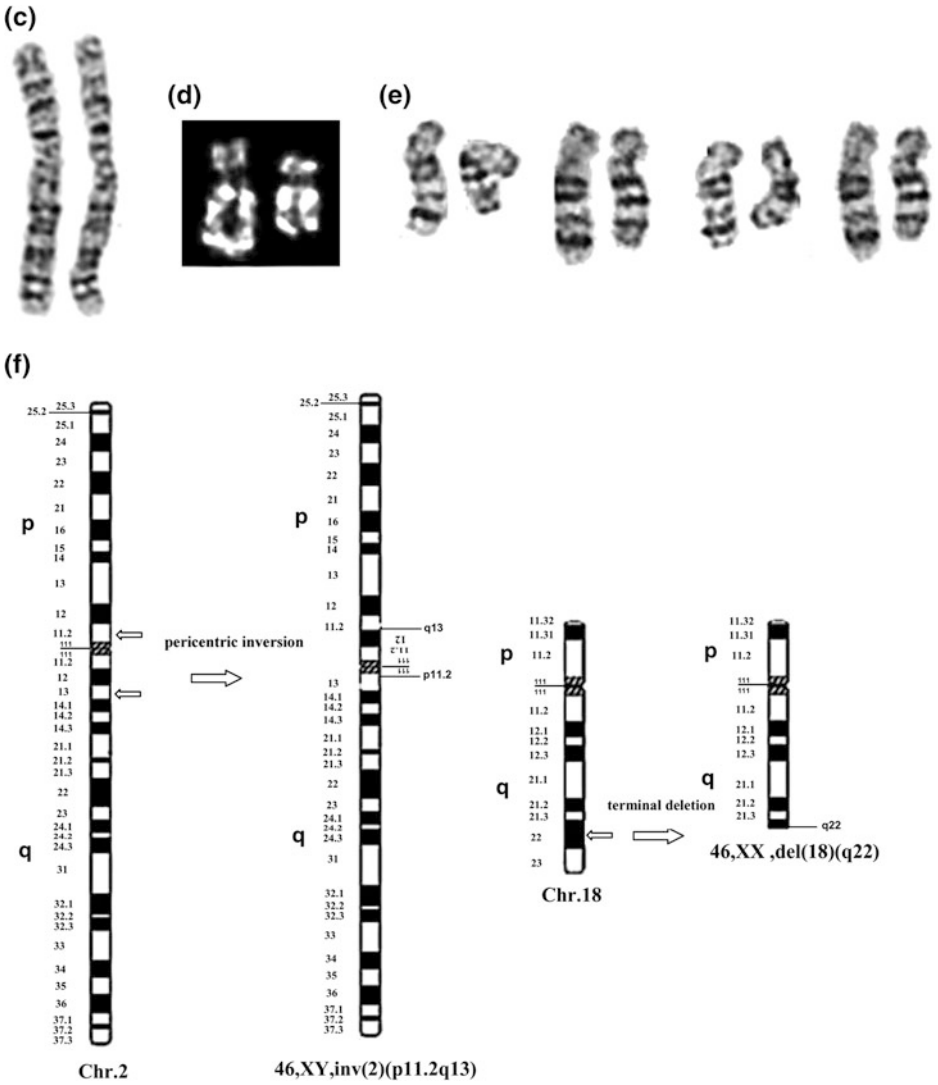

Fig. 4.83 (continued)

1. Pericentric inversion 2
   The rearrangement is balanced. One of the breakpoints (p11.2) is located at the border of pericentromeric heterochromatin and the first euchromatic band, whereas the second breakpoint is in the GC-rich euchromatic band q13.
   See Case 2
2. Deletion of chromosome 18
   The partial monosomy 18q can be defined as de Grouchy syndrome II, a well-known and frequent structural aberration.

Cave:

Even in cases of de novo structural chromosome aberrations (CCR) it must be excluded by microarray that the patient shows additional submicroscopic aberrations (Fig. 4.83).

Case 2: Karyotype: 46,XY,del(5)(q14.2q22.1),t(16;20)(q24;q13.11)

Indication for chromosome analysis: Developmental retardation, macrosomia, dysmorphic features.

Morphology:

The patient shows a complex chromosome rearrangement (CCR) involving 3 chromosomes and 4 breakpoints

1. Deletion 5q
   The phenotype of the child can be delineated from the interstitial deletion 5q.
2. Translocation 16/20
   The translocation 16/20 appears balanced.

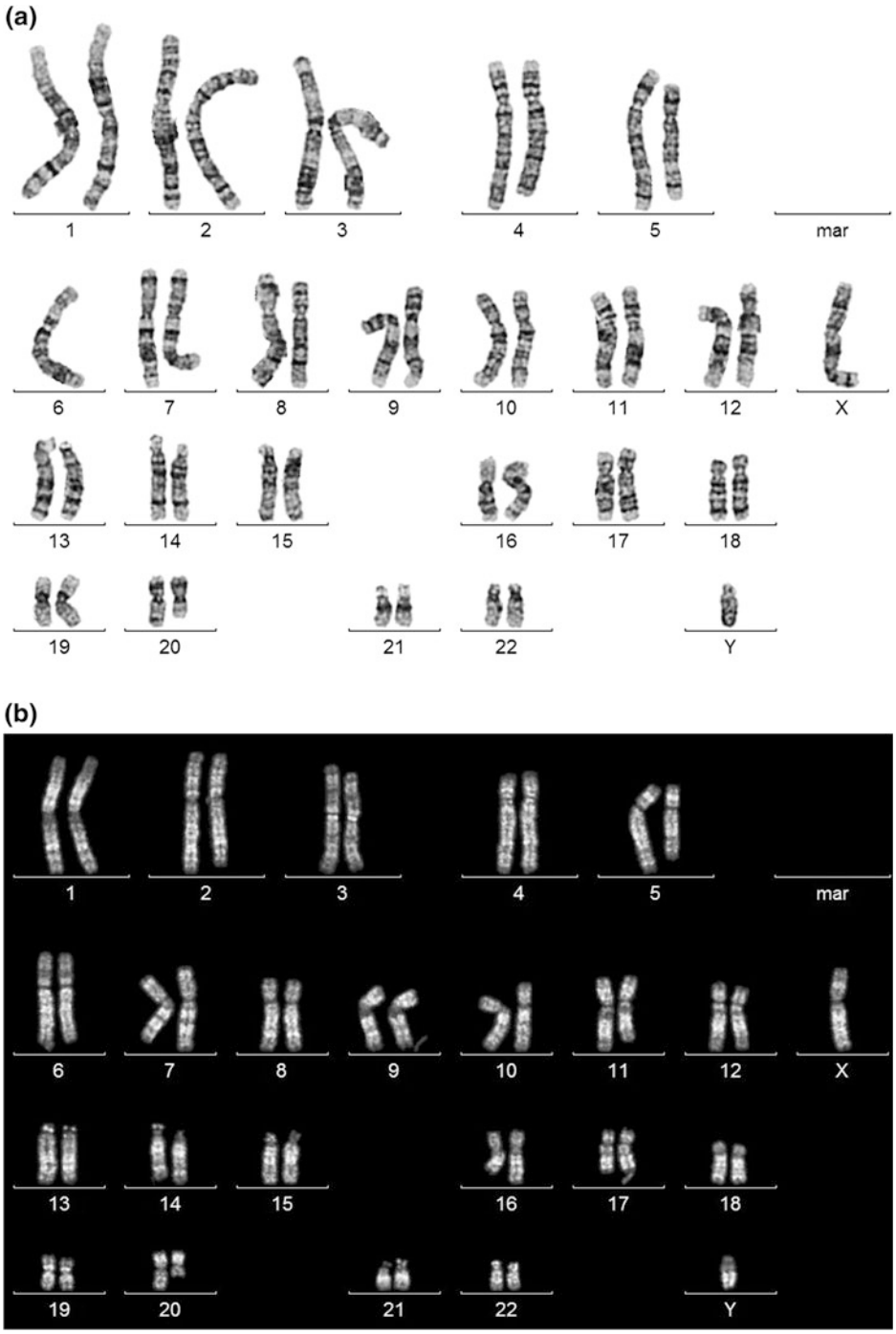

Fig. 4.84 Karyotype 46,XY,del(5)(q14.2q22.1),t(16;20)(q24;q13.11) with 1 chromosome 6 lost by preparation **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** GTG-banding, *left* normal, *right* deleted chromosome 5, **d** GTG-banding, *left* normal chromosomes 16 and 20, *right* translocation chromosomes, **e**, **f** ideograms of chromosomes 5, 16 and 20, chromosome 5 unbalanced rearrangement, chromosome 16 and 20 balanced translocation

Cave:

In the patient microarray analysis should be performed to exclude an additional submicroscopic aberration. The karyotype of both parents must be investigated before genetic counseling of the family (Fig. 4.84).

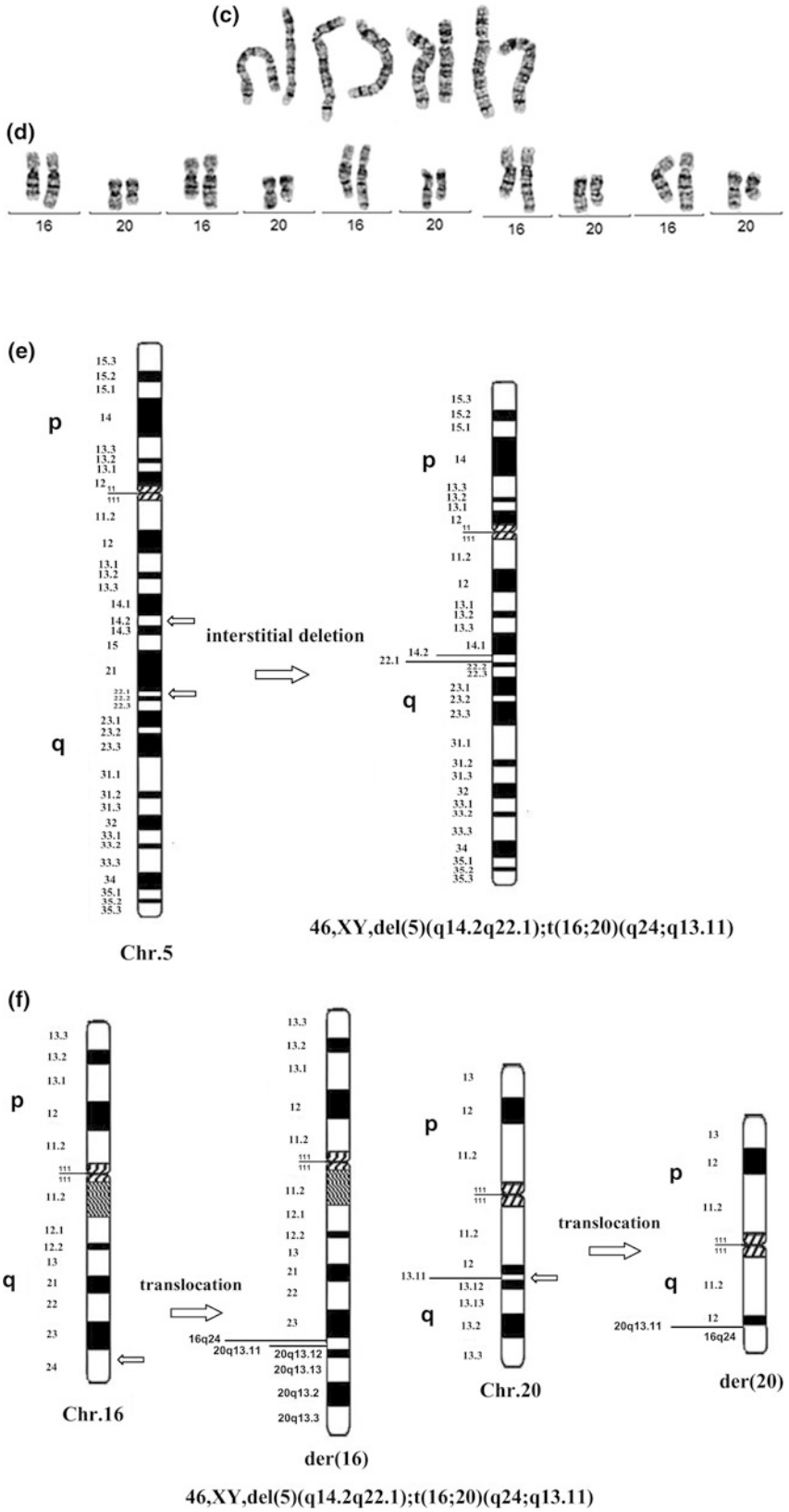

Fig. 4.84 (continued)

Case 3: Karyotype: 47,XY,inv(12)(q15q24.1),+dic,der(15)(pter→q11.2::q11.2→pter)
Indication for chromosome analysis: Increased number of abortions of the wife.

Morphology:

The complex chromosome abnormality consists of a paracentric inversion and an additional marker chromosome with 3 breaks in 2 chromosomes.

1. Paracentric inversion 12
   The inverted region comprises about 30% of the total length of chromosome 12. The genetic risk is low according to the literature.

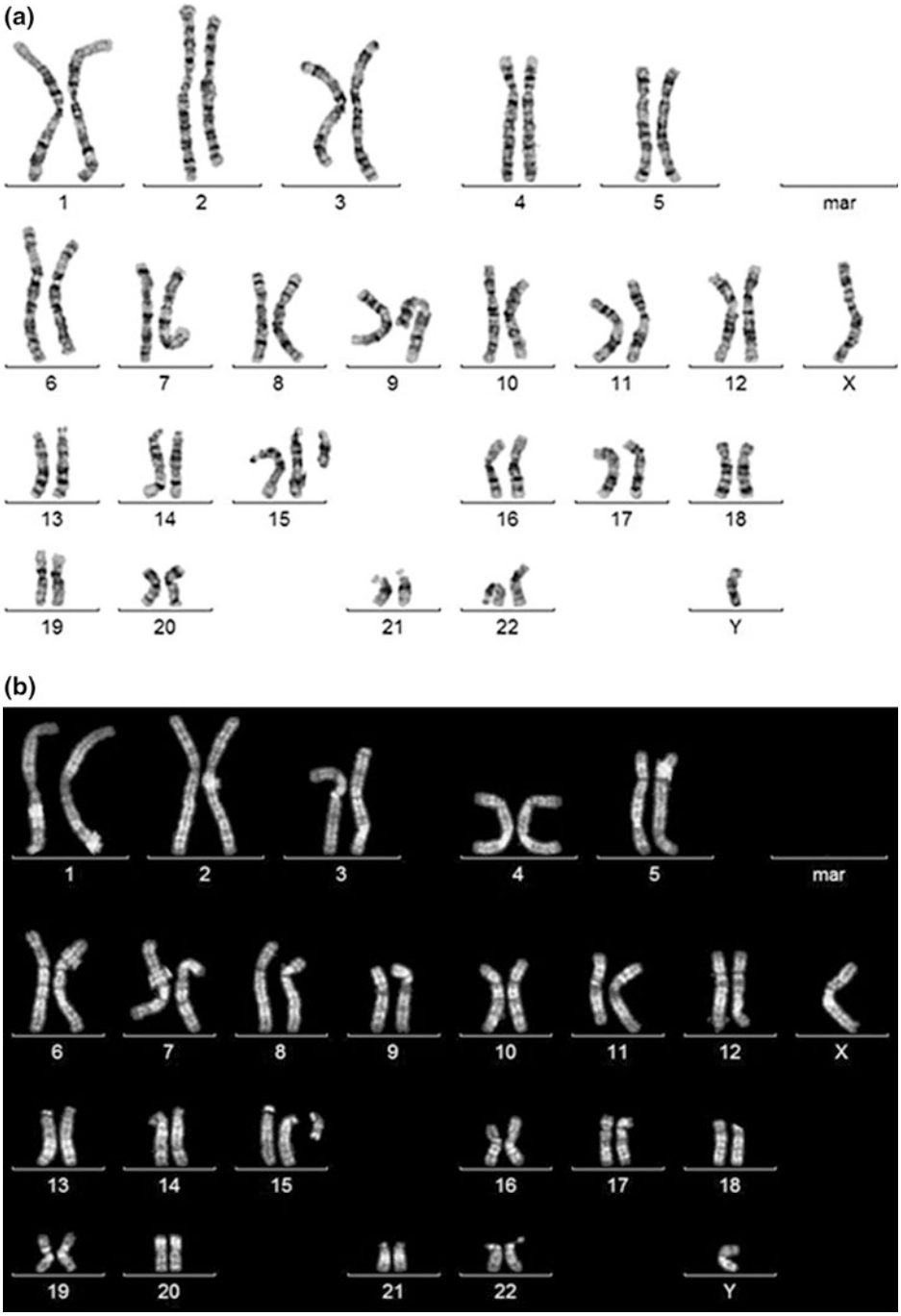

Fig. 4.85 Karyotype 47,XY,inv(12)(q15q24.1)+dic,der(15)(pter→q11.2::q11.2→pter), **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* normal chromosomes 12 and 15, *right* aberrant chromosomes, **e** ideograms from normal and aberrant chromosomes 12 and 15

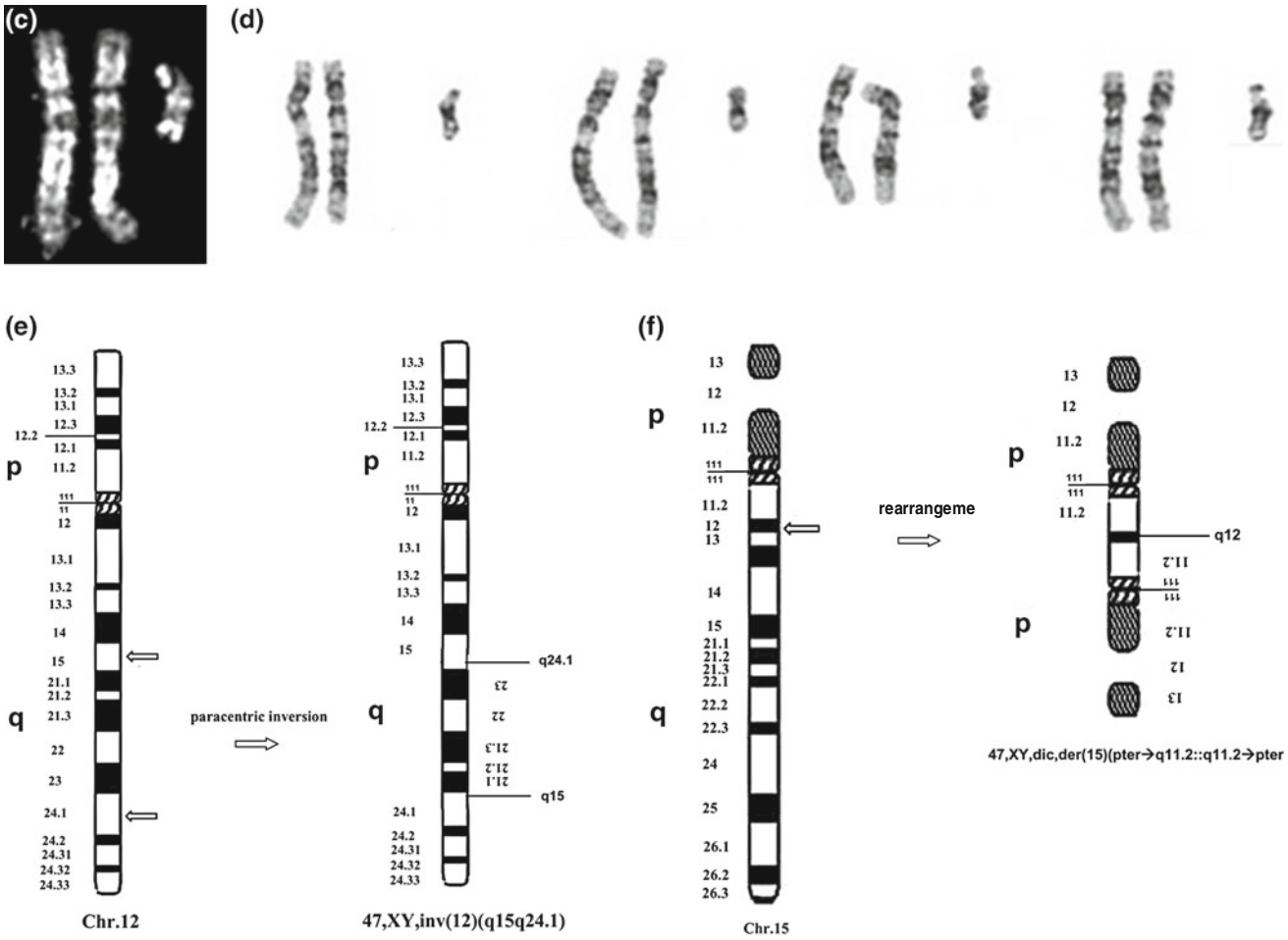

Fig. 4.85 (continued)

2. Additional marker chromosome der(15)
   The total derivative chromosome 15 consists of constitutive heterochromatin and is thus without relevance for the carrier himself.

Cave:

Prenatal diagnosis has to be offered to the couple, as the derivative chromosome 15 can lead to an unequal crossing over in meiosis and thus to UPD 15 (Fig. 4.85).

Summary

Three cases are presented in detail. All three of them can be assigned to the same subtype of aberration which comprises 2 different, independent structural abnormalities in the same karyotype. In the first case this is a deletion combined with a reciprocal translocation, in the second case a pericentric inversion is combined with a deletion, and in the third case a paracentric inversion is combined with a supernumerary heterochromatic marker chromosome. Only, when the chromosomes are analysed at a high structural resolution (at least 550 bands per genome), reliable diagnoses can be achieved in these complex cases. It has to be kept in mind that in familial cases during meiosis additional aberrations can develop.

4.2.2.4 Marker Chromosomes

1 47,XX,+der(14)(q10)
2 47,XY,+dic der(15)(pter→q11.1::q11.1→pter)
3 47,XX,+dic der(22)(q11.1)mat

Case 1: Karyotype: 47,XX,+der(14)(q10)
Indication for chromosome analysis: Genetic counseling because of the diagnosis of a marker chromosome in the mother.

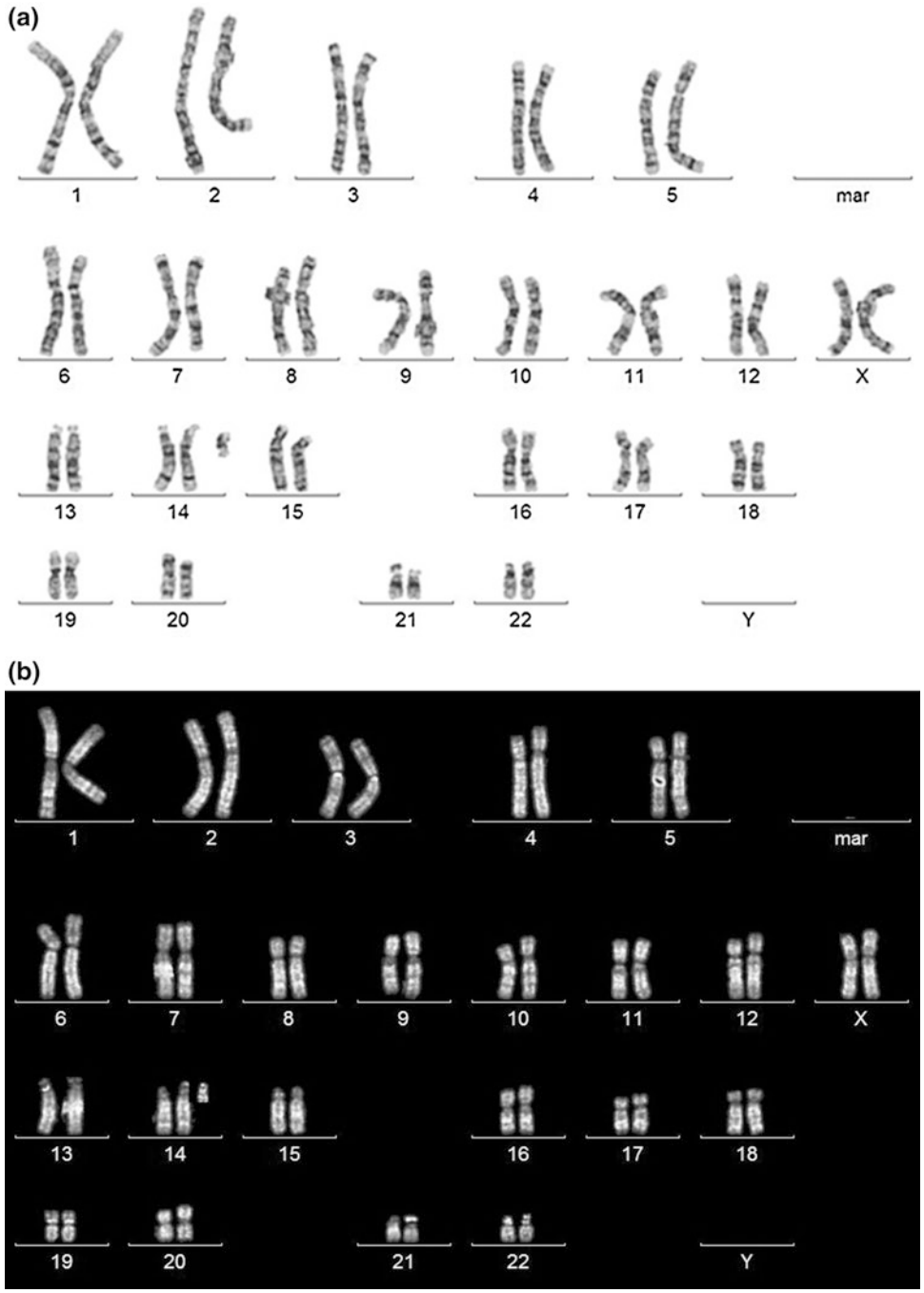

Fig. 4.86 Karyotype 47,XX,+der(14)(q10). **a** GTG-, **b** QFQ-banding, 550 and 400 bands per genome, **c** QFQ-, **d** GTG-banding, chromosomes from different mitoses, *left* 2 normal chromosomes 14, *right* der(14), **e** ideograms of normal chromosome 14 and der(14), the additional marker consists only of heterochromatic segments and therefore is without genetic relevance

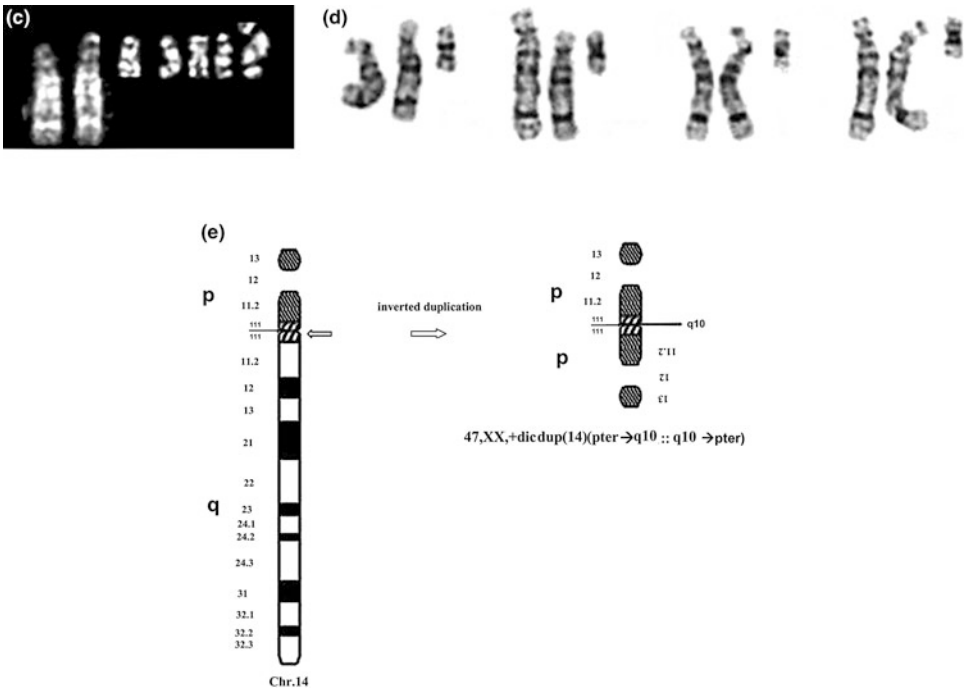

Fig. 4.86 (continued)

Morphology:

The derivate is heterochromatic, monocentric and consists of the complete short arms (p11.1 to p13) of the acrocentric chromosome, thus bearing satellites on both ends. The marker is not an isochromosome but can be delineated from 2 different chromosomes 14. The final analysis of the derivate required a FISH investigation.

Cave:

The marker is completely heterochromatic and thus of no relevance for the carrier herself. But in pregnancies it leads to an increased genetic risk:

- An unequal crossing over in meiosis I can lead to partial duplications or deletions of the proximal euchromatic long arm regions of chromosome 14.
- Malsegregation of a chromosome 14 in meiosis can be followed by trisomy or monosomy 14 and can lead after a regulation process to UPD 14.
- In some carriers (data from the literature) a reduced fertility was observed (Fig. 4.86).

Case 2: Karyotype: 47,XY,+dic der(15)(pter→q11.1::q11.1→pter)
Indication for chromosome analysis: Four years old boy with developmental peculiarities.

Morphology:

The additional marker chromosome is dicentric with one centromere inactivated. An exclusion of the occurrence of euchromatic segments and the final diagnosis were performed by FISH. The marker originated from 2 homologous chromosomes 15. In spite of its dicentric structure the marker was stable passing through somatic cell divisions. A second cell line was not observed.
Cave:

The chromosomes of the parents should be analysed, as all carriers of a heterochromatic derivate 15 have an increased genetic risk by the possible unequal crossing over in meiosis and by UPD 15 formation. As the developmental peculiarities of the child cannot be caused by the heterochromatic marker, further investigation should be performed (Fig. 4.87).

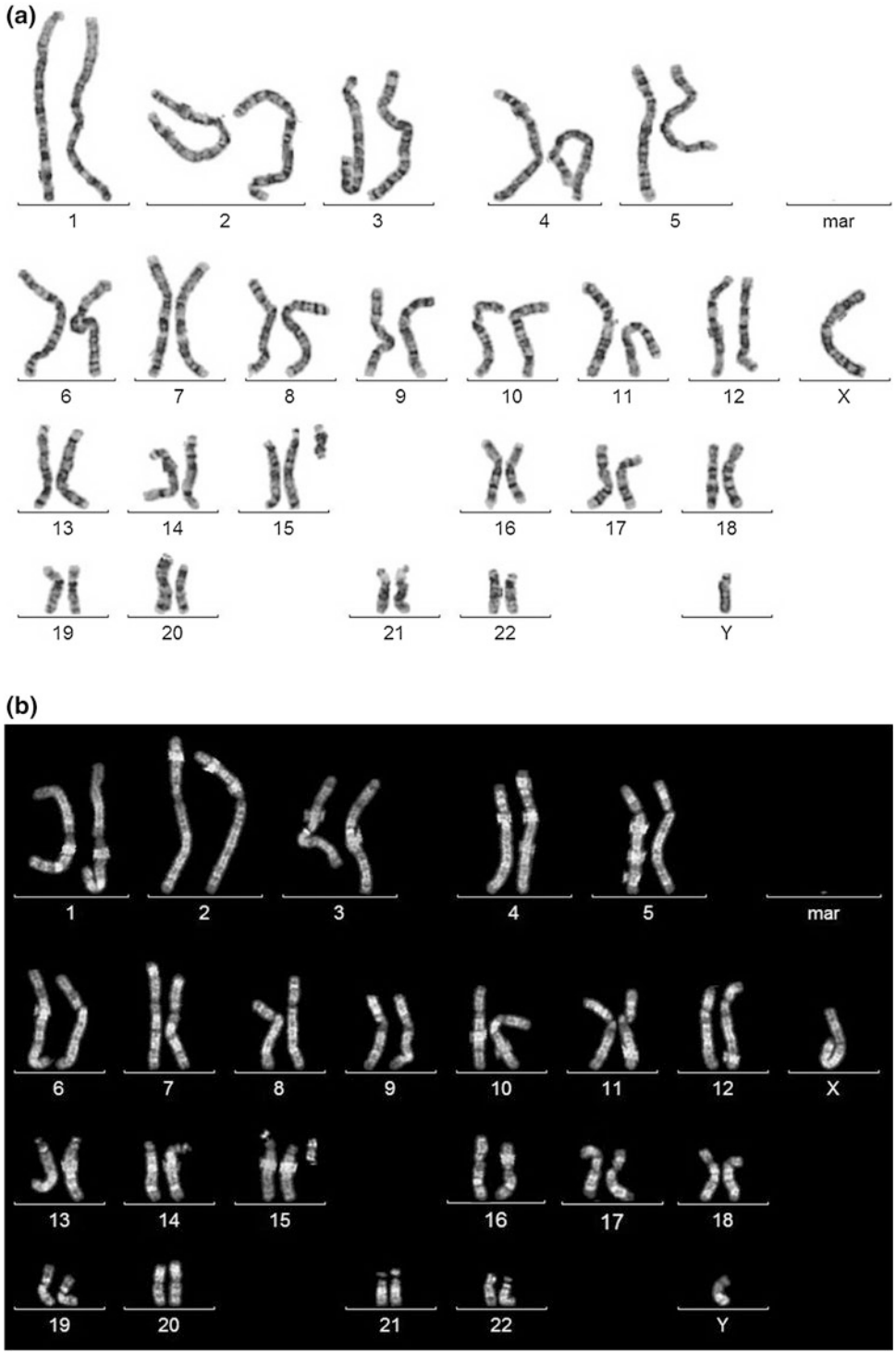

Fig. 4.87 Karyotype 47,XY,+dic der(15)(pter→q11.1::q11.1→pter). **a** GTG-, **b** QFQ-banding, 700 and 500 bands per genome, **c** CBG-, **d** QFQ-, **e** GTG-banding, chromosomes from different mitoses, **d**, **e** *left* normal chromosomes 15, *right* derivate 15, **c** derivate 15, **f** ideograms from chromosome 15 and derivate 15. der(15) is a completely heterochromatic marker, thus without genetic relevance for the carrier

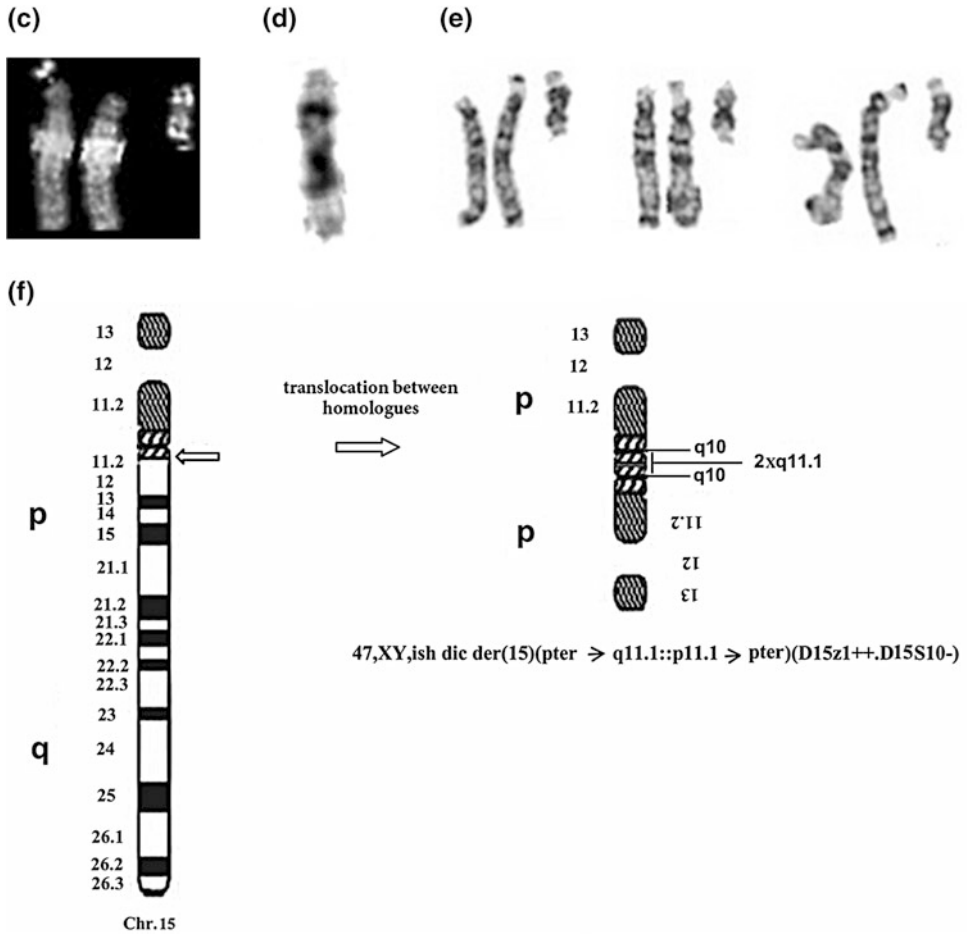

Fig. 4.87 (continued)

Case 3: Karyotype: 47,XX,+dic der(22)(pter→q11.1::q11.1→pter)mat

Indication for chromosome analysis: Prenatal diagnosis as the mother is carrier of an additional derivate 22.

Morphology:

The derivate 22 in mother and fetus are identic. The marker in the fetus is also heterochromatic, dicentric with inactivation of the second centromere. It originated by rearrangement from 2 homologous chromosomes 22.

Cave:

This child has to be informed when it is grown up by genetic counseling that it has an increased genetic risk independent of her age and that therefore prenatal diagnosis has to be offered in all pregnancies (Fig. 4.88).

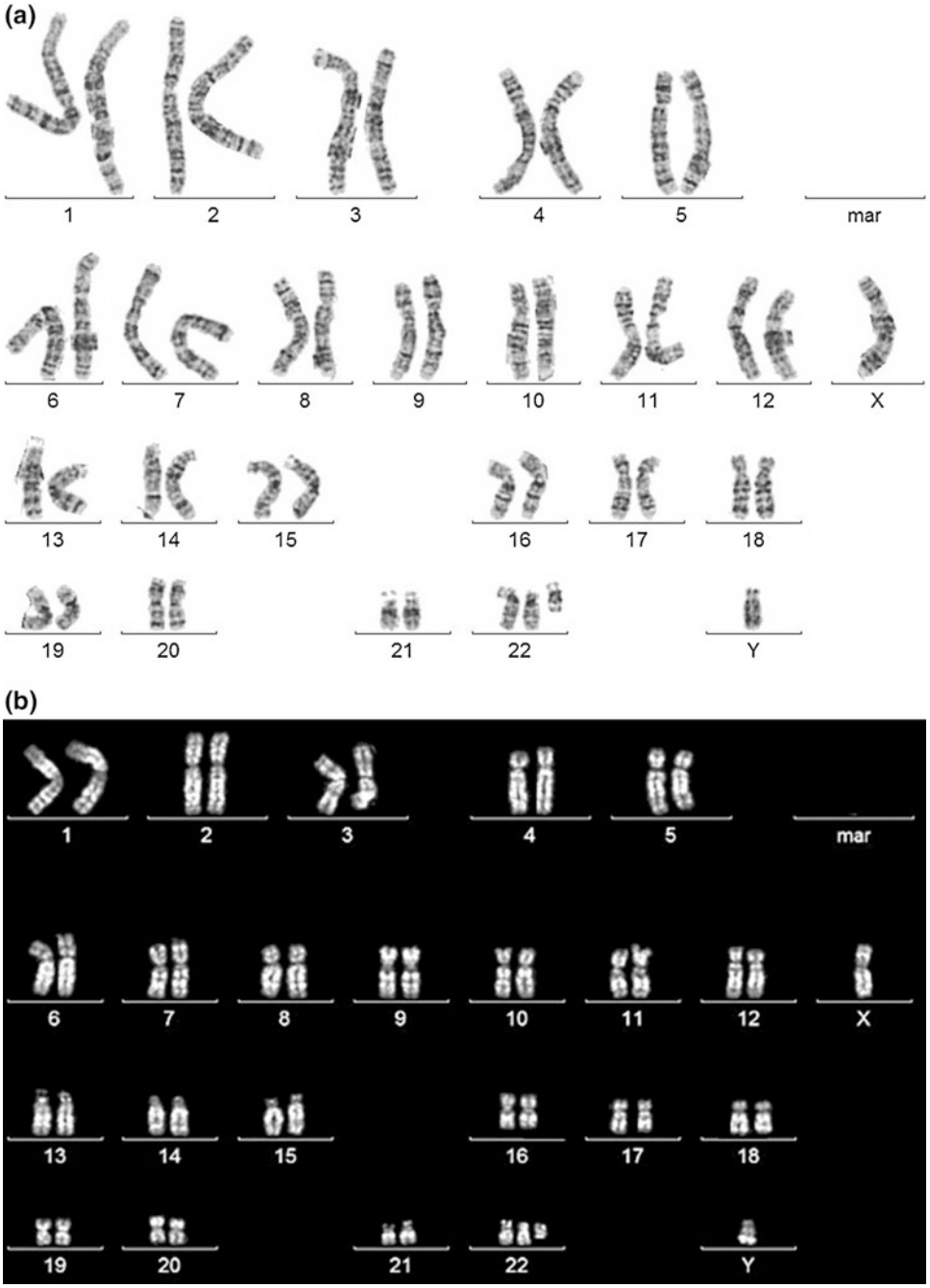

Fig. 4.88 Karyotype 47,XY,+dic der(22)(pter→q11.1::q11.1→pter)mat, **a** GTG-, **b** QFQ-banding, 700 and 400 bands per genome, **c** GTG-banding, chromosomes from different motoses, *left* normal chromosomes 22, *right* derivate 22, **d** ideograms from normal chromosome 22 and derivate 22, completely heterochromatic marker, thus without genetic relevance for the carrier

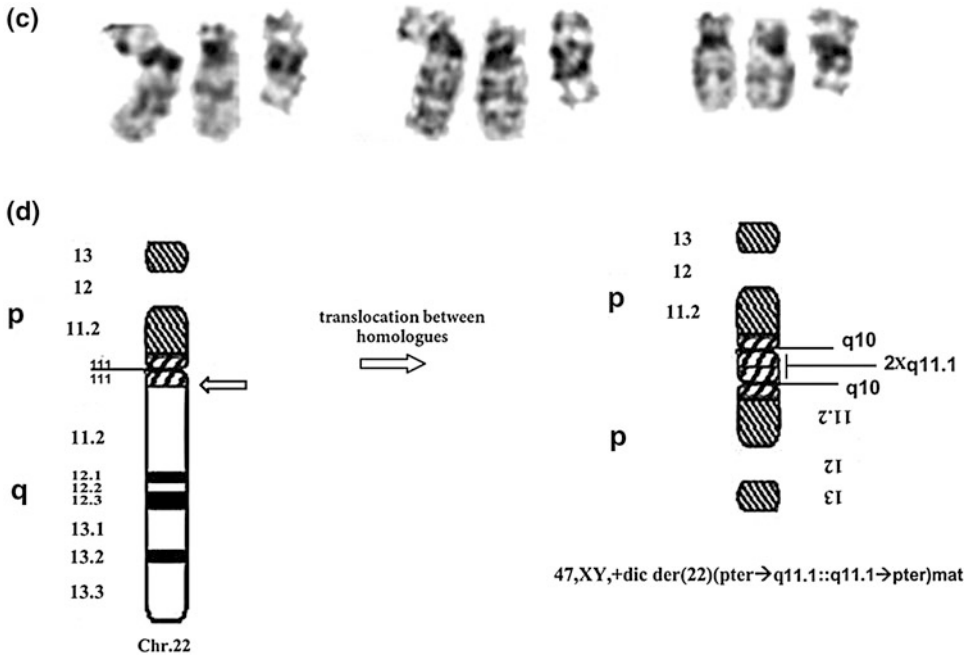

Fig. 4.88 (continued)

Summary

The three examples of marker chromosomes in this atlas are all together supernumerary derivates of the acrocentric, i.e. der (14), der(15), der(22). The first marker could be analysed as a derivate of chromosome 14. It is monocentric, with satellites on both ends and it is completely heterochromatic. It was familial in origin and derived from an inversion duplication. An isochromosome 14 could be excluded. The second marker is a derivate of chromosome 15, the most frequent origin of a marker. This der(15) is dicentric with one centromere inactivated, again originated from the two homologous chromosomes and with satellites on both ends. The occurrence of euchromatic segments between the two centromeres could be excluded (q11.2). The third marker is derived from chromosome 22. It originated from an inversion duplication and is completely heterochromatic with satellites on both ends. It can again be delineated from a rearrangement between two homologous chromosomes 22. The inactivation of the second centromere is complete, thus a second cell line is not present.

The diagnosis of the three supernumerary chromosome derivates required in addition to chromosome analyses FISH and microarray for a precise identification of the derivates and for the exclusion of euchromatic segments. Genetic counselling of the families has to include the risk of unequal crossing over in meiosis of the carrier which might lead to an unbalanced karyotype in the offspring.

Mutations in Non-coding-DNA Regions

5

(Synonyms: Polymorphic regions, structural variants, heteromorphisms)

In the following chapter frequent variants or polymorphisms are presented in an overview. As this Atlas gives examples on structural chromosome aberrations with clinical relevance, the role of variants is only to recognise, define and distinguish them from rearrangements in euchromatic regions.

The different types of variants are described and characterised in the introducing chapter of this Atlas.

5.1 Euchromatic Variants

Euchromatic variant within a heterochromatic block.

Morphology:

The proximal heterochromatin blocks 1q12, 9q12, 16q11.2 and the distal long arm region yq12 can be subdivided once or even several times. These interbands are CBG negative and can differ in size. They do not consist of genetic relevant euchromatin, which has been translocated by an inversion or insertion but consist of non-coding repetitive DNA sequences and are defined as genetic non relevant euchromatic heteromorphisms. In chromosomes 1q12, 16q11.2 and yq12 these interbands appear bright after GTG-banding while the interband in 9q12 appears dark.

Example:

The heterochromatic region 1q12 is subdivided by euchromatic polymorphic interbands. After CBG staining they appear light in the otherwise dark stained region. Even after GTG-banding the euchromatic interbands which differ in size are clearly diagnosable (Fig. 5.1, see also case 21, paracentric inversions).

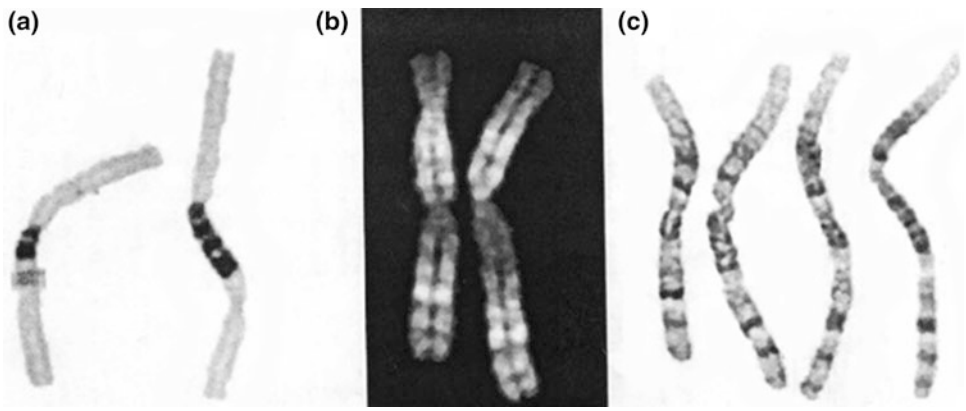

Fig. 5.1 Euchromatic variants presenting as light interbands in 1q12. **a** CBG-, **b** QFQ-, **c** GTG-banding, *left* normal chromosome, *right* amplification of 1q12 with euchromatic polymorphic interbands

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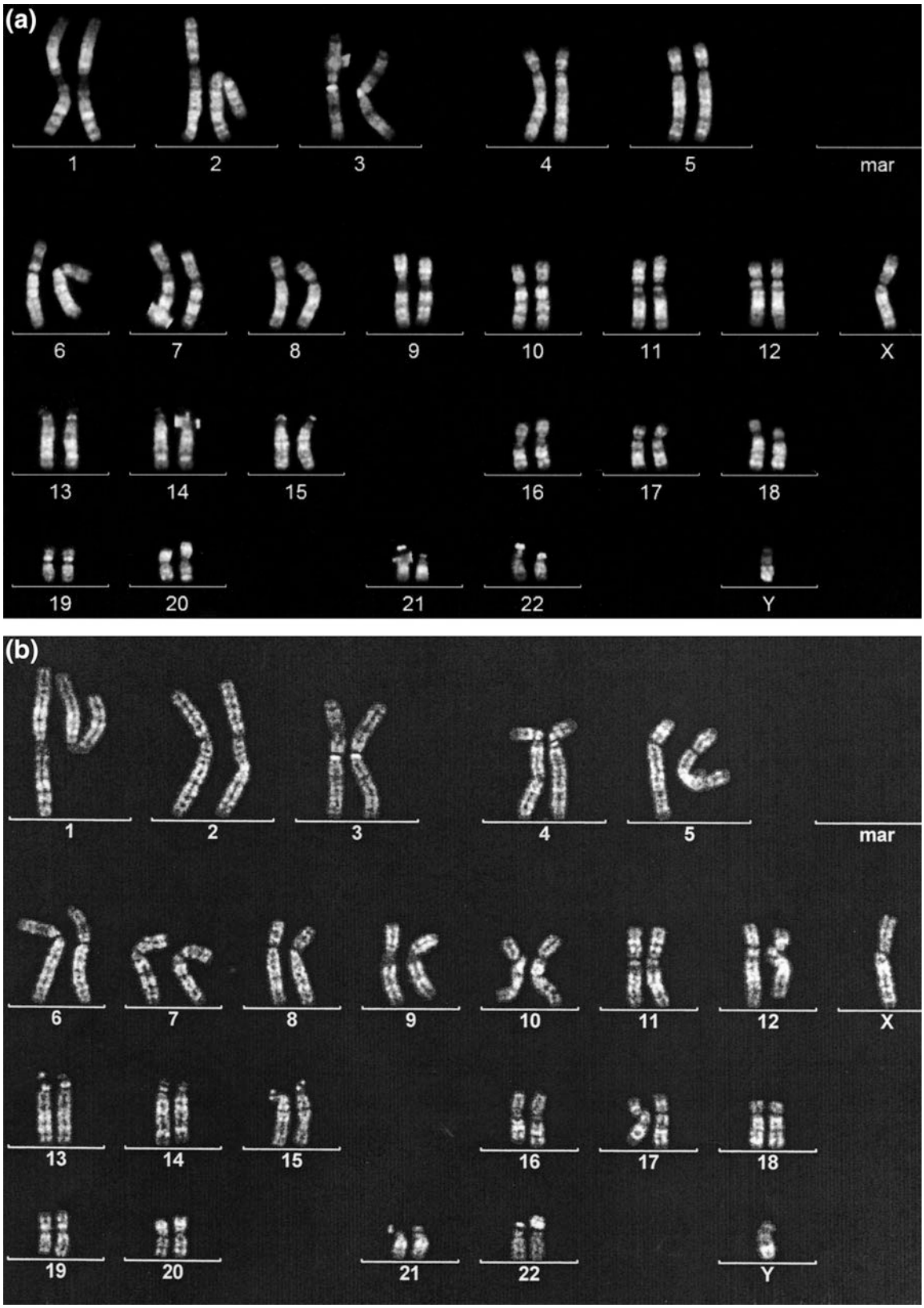

Fig. 5.2 **a** Metaphase after QFQ-banding Brilliant fluorescence in 14p13 (1 homologue), 15p13 (both homologues), 21p13 (both homologues), and 22p13 (both homologues). Besides, the size of p13 differs. **b** Amplification of the band 22p13 showing brilliant fluorescence (a translocation between Yq12 and 22p13 was excluded by FISH)

5.2 Satellites

The terminal regions (p13) of the acrocentrics can be duplicated, deleted or amplified without relevance for the carrier. Here we show a duplication of 13p13 after GTG and QFQ staining.
Example:

After QFQ-banding the satellites (p13) of the acrocentric chromosomes present with different fluorescence intensity (11–15 according to ISCN). The brighter fluorescence, also defined as brilliant (15) shows different frequency in its interchromosomal distribution (i.e. between 7 and 25% (Fig. 5.2a; see also: Case 36, paracentric inversion).

5.3 Nucleolus Organising Regions (NOR-Regions)

Examples:

Mutations in p12 of the acrocentrics are frequent. The region can be amplified, deleted or together with p13 duplicated or triplicated. The case presented here shows a triplication of 14p12 and p13 in a healthy carrier (Fig. 5.3).

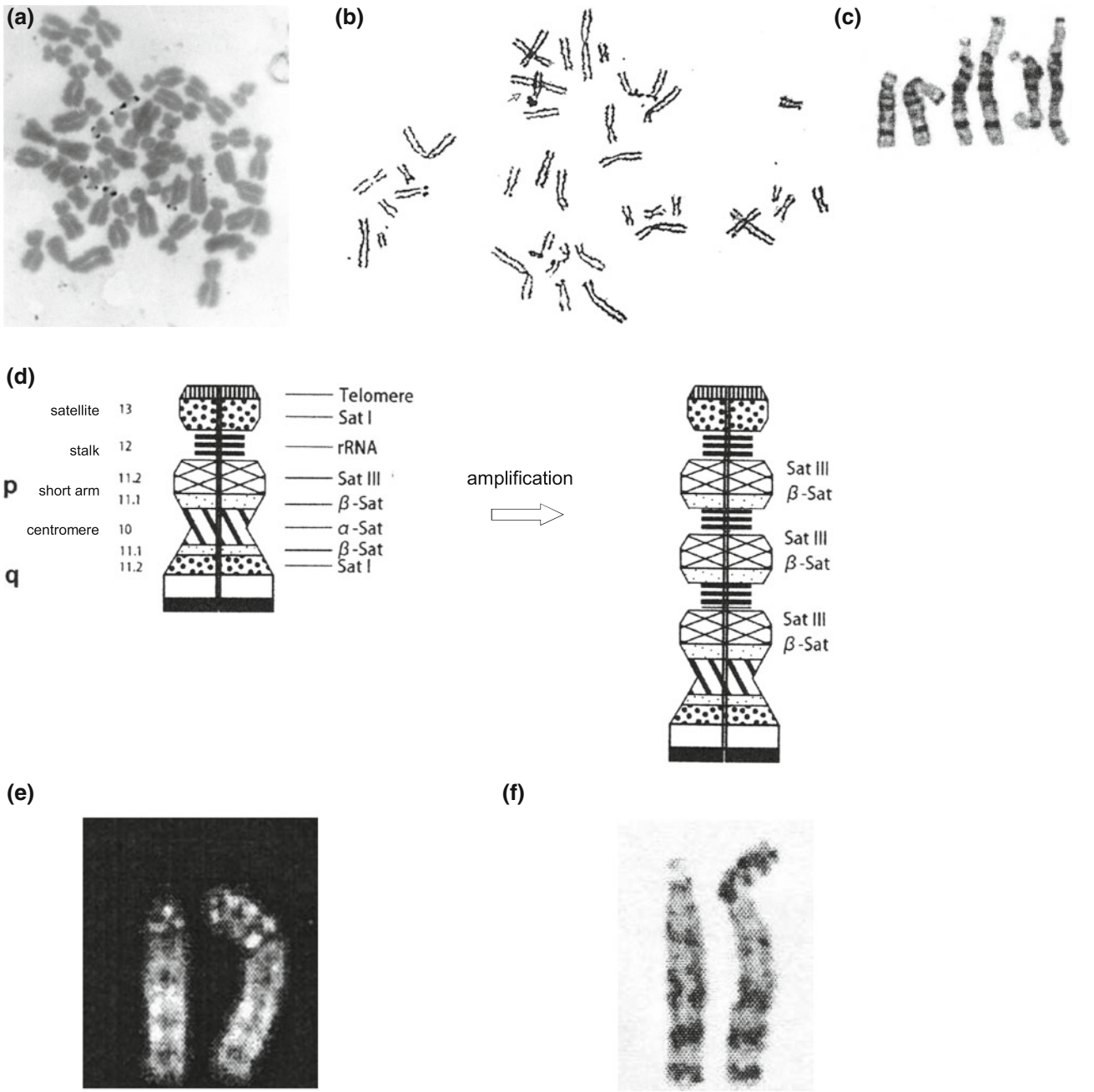

Fig. 5.3 **a** Metaphase after $AgNO_3$ staining showing NOR-regions (p12) of different size in the acrocentrics, Amplification of the NOR-region 14p12, **b** After NOR-staining, **c** GTG-banding of chromosomes from 3 different metaphases. The *right*, aberrant one, additionally shows puffing of p12. **d** Graph of the amplification 13p12, **e** QFQ-, **f** GTG-banding *left* normal, *right* aberrant chromosome 13

5.4 Pericentromeric Heterochromatin

Examples:

Neighbouring the centromere on both sides in the position p11 and q11, these bands can be decreased or increased in size. Often, together with the following heterochromatic band q11.2 they are involved in pericentromeric inversions such as 3q11.2, 4q11.2 and 19q11.2 (Fig. 5.4; see also the pericentric inversions: case 3 (chromosome 19), case 4 (chromosome 4) and case 16 (chromosome 3).

Diagnostic problems were given by deletions and duplications of 15q11.1 in times before the FISH area when the size of the region was misinterpreted and chosen as a diagnostic tool when investigating patients with clinical symptoms of Prader Willi or Angelman syndrome (Fig. 5.5).

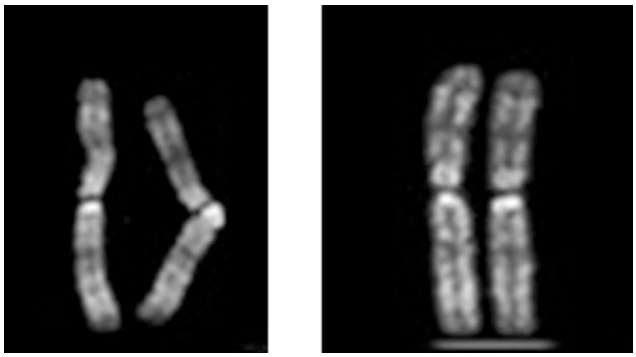

Fig. 5.4 Chromosome 3, QFQ-banding, *left* normal, *right* duplicated region in the proximal long arm [brilliant fluorescence i(5)]

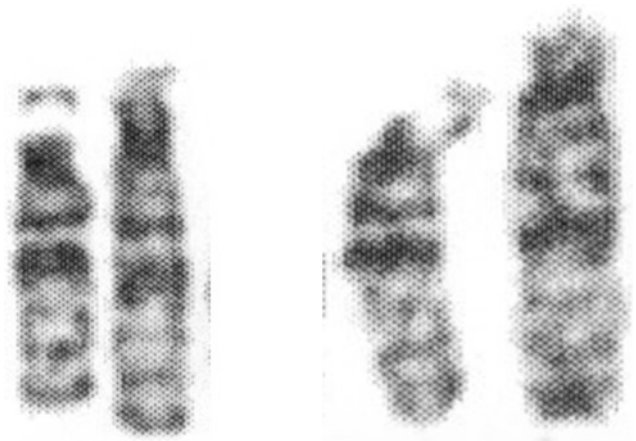

Fig. 5.5 Chromosome 15, GTG-banding chromosomes from different mitoses, *left* normal, *right* chromosome 15 with duplication 15q11.1

5.5 Centromere

Examples:

A dicentric chromosome with inactivation of one centromere is a well-known rearrangement of the X-chromosome (Fig. 5.6), in derivates of chromosome 15 (Fig. 4.87c–e) and in the Robertsonian translocation 13/14 (Fig. 4.81c–e). The size of the centromere can be reduced or enlarged, as it is often observed in chromosome 18 (Fig. 5.7).

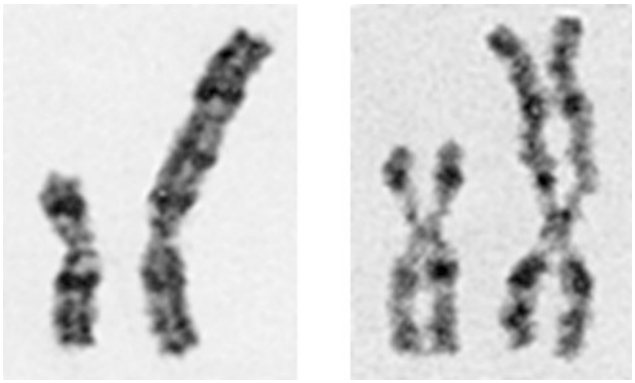

Fig. 5.6 X-chromosome from different mitoses, GTG-banding, *left* normal, *right* dicentric X-chromosome

Fig. 5.7 Chromosome 18 from different mitoses after GTG-banding, *left* normal, *right* aberrant chromosome with increased centromere region

5.6 Heterochromatic Blocks

Examples:

Mutations in the regions 1q12, 9q12, 16q11.2 and Yq12 show different types of rearrangement, their frequency depends on the population investigated (inversion 9q12 from 1 to 10%). The types of abnormalities are deletions, duplications, amplifications and partial and complete inversions. They are analysed after GTG, QFQ or CBG banding. Some are presented as examples combined with chromosome aberrations even in a homozygous status: see Chap. 4.

In addition we present here a duplication of 16q11.2 (Fig. 5.8) and an inversion in chromosome 9 (Fig. 5.9).

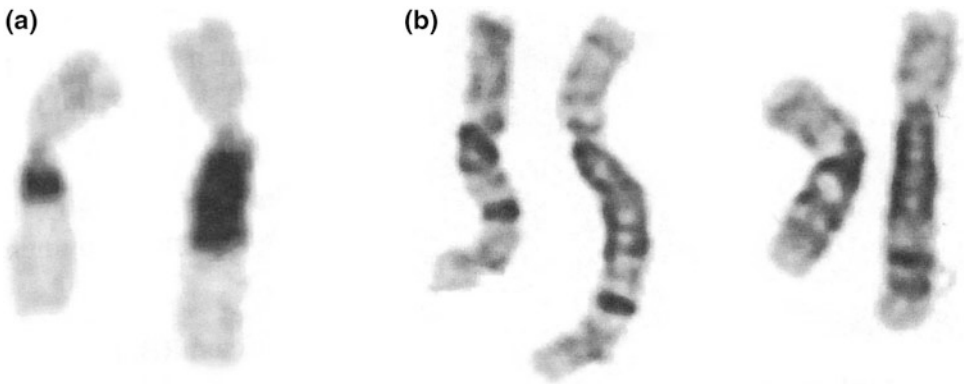

Fig. 5.8 **a** CBG-, **b** GTG-banding chromosome 16 from different mitoses, *left* normal, *right* aberrant chromosome 16 with amplification of 16q11.2

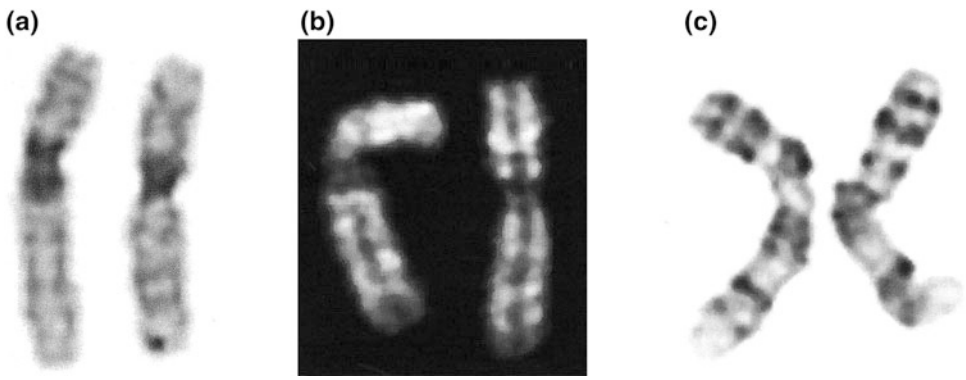

Fig. 5.9 **a** CBG-, **b** QFQ-, **c** GTG-banding of chromosome 9; chromosomes from different mitoses, *left* partial, *right* complete inversion of 9q12

Outlook

6

The results of the investigated cases presented in this Atlas with structural chromosome aberrations are based on the current given methological options to analyse the different types of abnormalities. It was particularly emphasized which spectrum should be chosen when combining the different techniques for the best way of diagnosis in the single case, for example direct preparation of cells and mitoses, short or long time cell culture, FISH, analysis of interphases, microarray, DNA-sequencing. In many cases family investigations and analysis of the pedigree should be performed additionally.

Generally it has to be taken into account, that the development of new and improved investigation methods is forthcoming. Thus, by improvement of diagnostic possibilities new fields of investigation will arise, and special groups of patients with cytogenetic analyses can be re-analysed under new research questions.

Thus, for example, constitutional aberrations of chromosome structure such as complex chromosome rearrangements (CCR) and abnormalities of tumor cells can be classified as anomalies originating from chromothripsis. Here additionally the relevance of the combination of cytogenetic and molecular genetic techniques is significantly enlightened.

Of special importance is the increasing number of analyses in the field of epigenetics. Functional aberrations caused by uniparental disomy (UPD) or by the inactivation of genes caused by changes in neighbourhood (position effects) are of increasing relevance especially in prenatal diagnosis.

Finally, maxims of ethical principles are playing an increasing role in the field of applied Cytogenetic when analysing inherited chromosome aberrations. It must be clearly defined to whom prenatal findings may be communicated (predictive diagnostics), may analyses be performed in children and adolescents (not legally able to consent). As to these problems legal regulation is increasing in various countries, but the requirements are not of uniform format.

For all human geneticists working in the field of applied Cytogenetics or on basic research it is already nowadays of essential relevance to develop a network of cooperation between university institutes and private laboratories to enable a regular exchange of experience, to establish regular specific congresses, seminars and workshops and to set up common projects.

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