

Chapter 2

Formation of UPD

Abstract Uniparental disomy (UPD) almost always arises in connection with a numerical or structural chromosomal aberration. UPD cases in which the causative cytogenetic event is still present, even if only in the mosaic state, provide deep insights into the abilities of gametes or embryonic cells to repair chromosomal imbalances and/or rearrangements. This chapter summarizes what is known on the formation of UPD in connection with triploidy, trisomy, monosomy, gamete complementation (Robertsonian) translocations, isochromosomes, and other rearrangements.

Uniparental disomy (UPD) can form due to a constitutional or acquired genetic change (Sect. 1.1.2.4). Obviously, chromosomal imbalances and/or rearrangements play a major role in UPD formation (Sects. 1.1.2.5 and 1.3.2). Generally speaking:

- Genome-wide UPD is thought to arise in connection with an initially normal karyotype, triploidy or gamete complementation (Sects. 2.1 and 2.3.1.1).
- Chromosomal UPD can be due to trisomic rescue (Sects. 2.1 and 2.3.1.2), monosomic rescue (Sects. 2.1 and 2.3.2.1), gamete complementation (Sects. 2.1 and 2.3.2.2), or in connection with chromosomal rearrangements (Sects. 2.2 and 2.3.2.2).
- Segmental UPD may appear due to any kind of structural rearrangement (Sects. 2.1, 2.2.4 and 2.3.2.4), which can be of parental origin or from de novo events during gametogenesis, early embryogenesis, or (if restricted to one or a few tissues) later in the life of the individual (Yamazawa et al. 2010).

When discussing UPD formation, the terms meiosis I, meiosis II, and post-zygotic (i.e. postfertilization) errors and “mitotic recombination” are mentioned repeatedly in the literature (Yamazawa et al. 2010). Meiosis I and meiosis II errors are also sometimes called “primary UPD” and “secondary UPD,” respectively (Fernández-Rebello et al. 2010). These designations are mainly applied to discuss diagnostic results, and they are considered to be helpful for the interpretation of possible modes of UPD formation (Sect. 2.5).

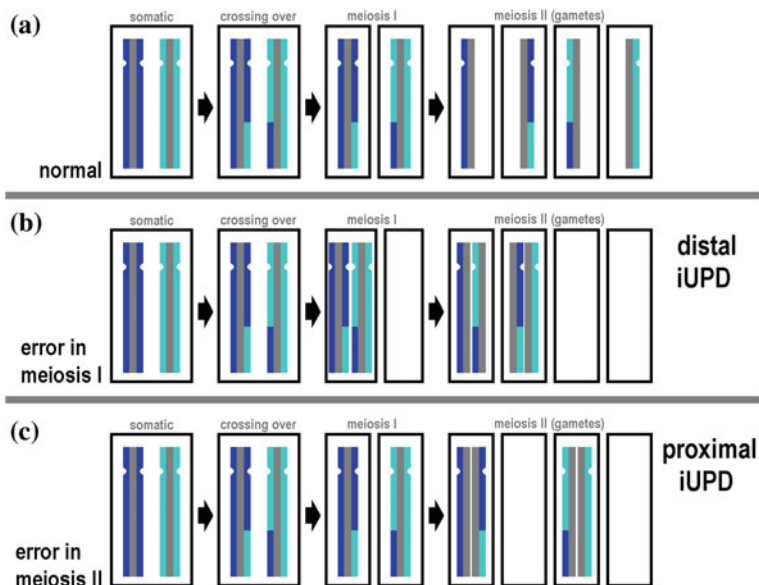


Fig. 2.1 A chromosome pair undergoing male meiosis is depicted. **a** The chromosome pair undergoes meiosis, including crossing over, with a balanced outcome. **b** The chromosome pair passes meiosis with crossing over but meiosis I error. Thus, two disomic and two nullisomic gametes are formed. If disomic gametes come to fertilization, trisomy is formed. If trisomic rescue happens, a distal iUPD is present. **c** The chromosomes sustain a meiosis II error, which leads to a similar situation as in Fig. 2.1 **b**. However, in case of trisomic rescue, pericentric (i.e. proximal) iUPD is present. Due to the different regions of iUPD, differentiation of meiosis I and meiosis II errors in h/iUPD cases may be possible. See also Fig. 2.11

For example, 25 % of female UPD(15) mat cases showed a nonrandom, skewed X-chromosome inactivation; for those cases, a postzygotic formation may be suggested (Robinson et al. 2000). The latter finding also aligns with the observations that (i) chromosomal imbalances are frequently seen in the early stages of embryogenesis (Martin et al. 1987; Evsikov and Verlinsky 1998) and (ii) UPD formation due to chromosome loss and reduplication was repeatedly observed in embryonic stem cells (Cervantes et al. 2002).

Figure 2.1 shows how meiosis I and meiosis II errors can be distinguished in h/iUPD cases. If iUPD regions are distal, the error occurred in meiosis I. If iUPD is pericentric or more proximal, it was a meiosis II error (Gardner and Sutherland 2004). This simplistic idea may be true for some but not all UPD cases (see Sect. 2.3.1.2), as it is now known that “the situation is more complicated” (Hassold et al. 2007).

UPD is also seen in different chromosome-specific frequencies. UPD(15) is present in 1 out of 80,000–100,000 births, segmental UPD(11) pat is present in 1 out of 75,000 live births, and UPD(6) pat is present in 1 out of 1,250,000 births

(Robinson 2000). This may be a result of prenatal selection against specific UPDs and/or chromosome-specific features, such as size or positioning in the interphase nucleus (Manvelyan et al. 2008).

2.1 Normal Karyotype and UPD

Irrespective of the aforementioned facts in this chapter, approximately 65 % of comprehensively studied UPD cases present with a normal karyotype (Chap. 1). Still, in case of whole genomic, chromosomal, or segmental UPD, the presence of an initial chromosomal imbalance that was later corrected to a normal karyotype is most likely. In other words, most (if not all) UPD cases with normal karyotypes are the result of an abnormal genetic constitution of a precursor cell.

Furthermore, a normal karyotype detected in one tissue of a patient, most often peripheral blood or fibroblasts, does not mean that cryptic aberrations can be excluded in general. Chromosomal changes may be mosaic trisomies that are only detectable by array-based comparative genomic hybridization (aCGH; Rodríguez-Santiago et al. 2010) or by studies of other tissues from the UPD patient (Chan et al. 2000). Also, submicroscopic microdeletions may be causative for UPD-related syndromes, such as Prader-Willi syndrome (PWS) or Angelman syndrome (AS; Liehr et al. 2005). In summary, a normal karyotype detected in the routine analysis of a UPD patient is not at all proof of a diploid chromosomal constitution in all ~400 different tissues in the human body.

As stated by Wendy P. Robinson in 2000:

UPD may arise from a completely normal cell line (at least) by either of two mechanisms: a loss of one chromosome followed by duplication of the remaining homologue or through somatic recombination event. A reciprocal exchange would lead to a region of isodisomy between the point of recombination and the telomere of the daughter cells, whereas a gene conversion event could lead to a small region of isodisomy anywhere along the chromosome arm. Loss of heterozygosity due to somatic recombination was first shown to occur in *Drosophila* in 1936 and has since been demonstrated in many organisms including mammals. Somatic recombination events would normally be difficult to detect in vivo as both maternal and paternal UPD daughter cells should be produced and uniparental inheritance would not be detected with conventional molecular approaches

Interestingly, even whole-genomic UPD may develop from a numerically normal zygote (Sect. 2.3.1.1).

2.1.1 Segmental UPD in a Normal Karyotype

A normal karyotype together with segmental UPD is most often found in Beckwith-Wiedemann syndrome (BWS) (Sect. 4.3). In these patients, UPD may be present in mosaic pattern as well (Sect. 2.4). Other known segmental UPDs are

listed in the chromosome-specific sections of this book. Overall, segmental UPD (shown in Fig. 2.1d) is thought to be due to a somatic recombination during mitotic cell division. This so-called mitotic crossing-over is rare in healthy somatic cells, but it happens regularly in cancer development (Cavenee et al. 1983).

2.2 Aberrant Balanced Karyotype

The most frequently observed balanced cytogenetic aberration in all cells of UPD patients is the translocation of two different chromosomes (Sect. 2.2.1). Furthermore, isochromosome formation (Sect. 2.2.2) and other rearrangements (Sect. 2.2.3) are balanced rearrangements. By definition, all aberrant balanced karyotypes in connection with UPD are segmental; this aspect is discussed in more detail in Sect. 2.2.4.

2.2.1 Translocations

The nonhomologous reciprocal exchange of two chromosomes is called a balanced chromosomal translocation event. It may appear between homologous or nonhomologous chromosomes; however, normally only the latter can be recognized cytogenetically (Fig. 2.2a). Such translocations can involve arbitrary breakpoints along each chromosome, even though hot spots of recombination were already suggested (Engel 2006) and reported (Manvelyan et al. 2007; Liehr et al. 2011; Bhatt et al. 2014).

Balanced translocations (including Robertsonian translocations; see Sect. 2.2.1.1) are present in 1 of 500 individuals in the normal population (Gardner and Sutherland 2004). The main problem of translocation carriers is the advanced risk for an unbalanced situations in offspring, which may lead to early abortion or children with clinical symptoms (e.g. Liehr et al. 2004). Even though the risk for an abortion or affected child is as high as 50 %, such translocations can be stable in populations for centuries (Koskinen et al. 1993). In addition, hUPD can arise in the offspring of balanced translocation carriers, which is only recognized as problem if a chromosome subject to imprinting is involved (e.g. Behnecke et al. 2012; see Fig. 2.2a).

The frequency of UPD in the offspring of balanced translocation carriers is not known. Because molecular tests are performed only in clinically abnormal individuals, just 11 such cases are reported (Table 2.1). Also, unbalanced translocation carriers may show segmental UPD (Sect. 2.3.1.4; Fig. 2.2b). One reported case supports the idea that trisomic rescue is involved in UPD formation in familial balanced translocations (Wang et al. 1998).

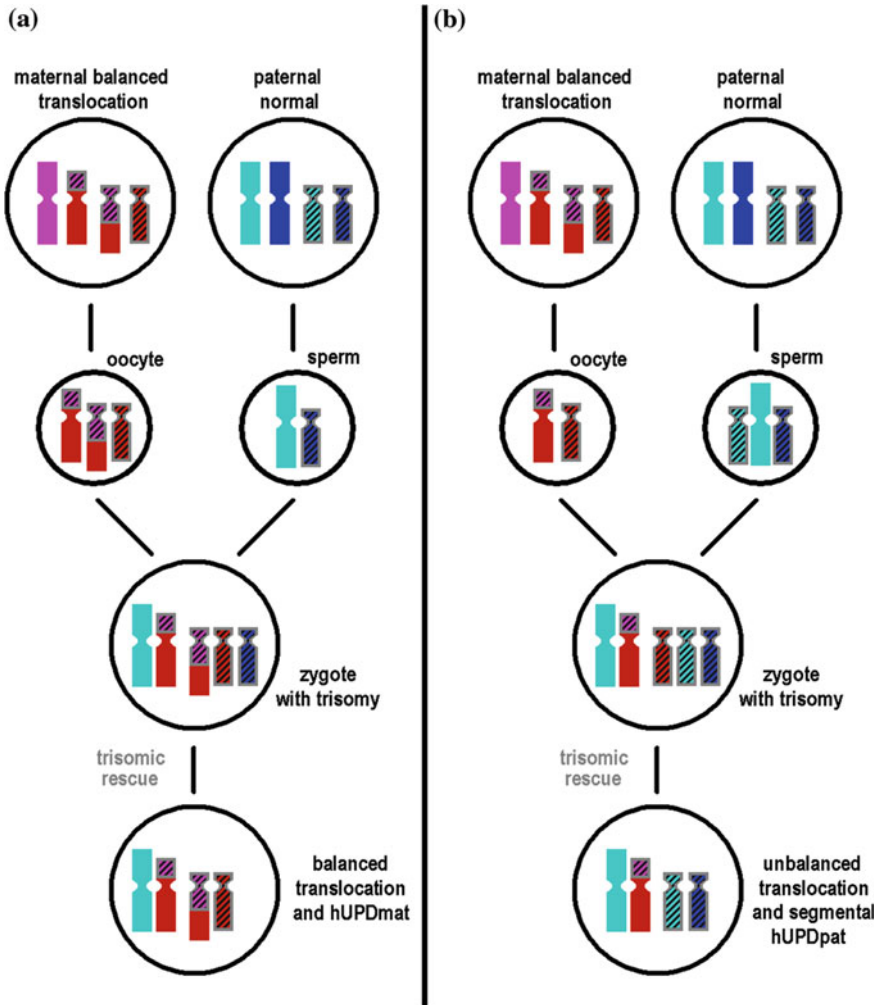


Fig. 2.2 Possible consequences of a parental balanced translocation in connection with UPD. **a** A parental balanced translocation may lead to an imbalanced disomic gamete, which, if involved in zygote formation, may be trisomic. If trisomic rescue takes place, a balanced karyotype together with UPD may result. **b** When an unbalanced gamete derived from the translocation carrier meets a disomic partner, another kind of trisomic zygote is formed. Trisomic rescue may lead here to an imbalanced outcome and UPD

2.2.1.1 Robertsonian Translocations

As defined by Robinson et al. (1994), “Robertsonian translocations are whole-arm exchanges between acrocentric chromosomes, which, in humans, occur between chromosomes 13, 14, 15, 21 and 22. These are the most frequent chromosomal rearrangements in man, with an estimated frequency in newborn of about 1/900.”

Table 2.1 Cases with hUPD in connection with a balanced translocation

UPD	Karyotype	Case number according to Liehr (2014c)
UPD(7)mat	46,XX,t(7;16)(q21;q24)mat	07-WmU-bal/1-1
UPD(7)mat	46,XX,t(7;13)(q11.2;q14)mat	07-WmU-bal/3-1
UPD(15)mat	46,XY,t(2;15)(p11;q11.2)mat	15-WmU-bal/4-1
UPD(15)mat	46,XY,t(8;15)(q24.1;q21.2)mat	15-WmU-bal/5-1
UPD(15)mat	46,XY,t(3;21)(p13;p11.2)mat	15-WmU-bal/6-1
UPD(15)mat	45,XX,der(6)t(6;15)(p25.3;q11.1)pat, -15 (microdeletion in 15q13.1 pat suggested)	15-WmU-bal/7-1
UPD(15)pat	45,XX,der(6)t(6;15)(p25.3;q11.1)pat, -15	15-WpU-bal/4-1
UPD(15)pat	45,XY,t(8;15)(p23.3;q11)pat	15-WpU-bal/5-1
UPD(16)mat	46,XY,t(10;16)(q11.2;q11.1)mat[22]/47,idem, +16[4]	16-WmU-imb/5-1
UPD(20)pat	46,XX,t(11;20)(p13;p13)mat	20-WpU-seg-q13.2/1-1

Note Ten out of ten reported cases were parentally derived

In Robertsonian translocations, two short arms of the involved acrocentric chromosomes are lost. However, as this is harmless for the carrier, Robertsonian translocations are considered to be balanced chromosomal rearrangements within the cytogenetic community.

According to Ruggeri et al. (2004), approximately 4 % of Robertsonian translocations are associated with a UPD. Still, in Robertsonian translocations, it is important to distinguish rearrangements with nonhomologous chromosomal partners from those with homologous chromosomal partners (Fig. 2.3). In nonhomologous Robertsonian translocations, UPD risk was estimated to be 0.6 % (Ruggeri et al. 2004). The formation of hUPD in the case of an inherited Robertsonian translocation is depicted in Fig. 2.3a.

Homologous Robertsonian translocations normally are isochromosomes (i.e., chromosomes derived from a duplication of a single parental chromosome) and are thought to develop due to monosomic rescue (Fig. 2.3b; Sect. 2.3.2.2.2). In addition, homologous Robertsonian translocations may form due to a crossing-over error in meiosis I; then, as a consequence, they lead to a hUPD (not depicted). In contrast to the data from Ruggeri et al. (2004), who only knew of UPD in de novo cases, it is now known that UPD may appear in Robertsonian translocations with de novo formation (40 % of the cases) and in inherited cases (60 % of the cases) (Liehr 2014c).

Robertsonian translocations with UPD and an additional sister chromosome have been reported only twice; however, both cases were iUPD(13) (Soler et al. 2000; Berend et al. 2000).

Most frequently reported in association with Robertsonian translocations are UPD(14) and UPD(15). Between 1 and 50 % of those cases are associated with a Robertsonian translocation (Table 2.2). There must be a yet-unknown biology behind the finding that Robertsonian translocations and UPD(14) mat are much more frequently associated than is the case with UPDs in other acrocentric chromosomes.



Fig. 2.3 **a** hUPD in connection with an inherited Robertsonian translocation may form, similar to the mechanism shown for translocations in general in Fig. 2.2a. **b** iUPD is thought to form de novo in connection with a monosomic rescue process

Tab 2.2 Cases with Robertsonian translocation in the most frequent UPD syndromes of acrocentric-derived chromosomes and the percentages of homologous and non-homologous recombination (Liehr 2014c)

	with Robertsonian translocation [%]	Homologous recombination [%]	Non-homologous recombination [%]
UPD(14)mat	50	40	60
UPD(14)pat	15	60	40
UPD(15)mat	1	50	50
UPD(15)pat	15	60	40

Table 2.3 Derivative chromosomes formed due to Robertsonian translocations and associated UPDs according to Liehr (2014c)

UPD type	Karyotype	Number of reported cases
UPD(13)mat	45,XN,der(13;13)(q10;q10)	3
UPD(13)pat	45,XN,der(13;13)(q10;q10)	4
UPD(14)mat	45,XN,der(13;14)(q10;q10)	14
	45,XN,der(14;14)(q10;q10)	14
	45,XN,der(14;15)(q10;q10)	1
	45,XN,der(14;21)(q10;q10)	4
	45,XN,der(14;22)(q10;q10)	1
UPD(14)pat	45,XN,der(13;14)(q10;q10)	4
	45,XN,der(14;14)(q10;q10)	5
UPD(15)mat	45,XN,der(13;15)(q10;q10)	2
	45,XN,der(14;15)(q10;q10)	4
	45,XN,der(15;15)(q10;q10)	5
UPD(15)pat	45,XN,der(13;15)(q10;q10)	4
	45,XN,der(14;15)(q10;q10)	2
	45,XN,der(15;15)(q10;q10)	8
UPD(21)mat	45,XN,der(21;21)(q10;q10)	2
UPD(21)pat	45,XN,der(21;21)(q10;q10)	2
UPD(22)mat	45,XN,der(22;22)(q10;q10)	4
UPD(22)pat	45,XN,der(22;22)(q10;q10)	1

In addition, homologous and nonhomologous recombination can be observed in all four groups in equal distribution of about 1:1 (Table 2.2). Thus, the suggestion from the literature that Robertsonian translocations between homologous chromosomes are much more likely to lead to UPD than those between nonhomologous chromosomes (Ruggeri et al. 2004; Bruyère et al. 2004) seems not to be valid according to this data (Table 2.2; Liehr 2014c).

In Table 2.3, the chromosomes involved in Robertsonian translocations in relation to corresponding UPDs are listed. Most likely, an assessment bias has to be considered here.

2.2.2 Complementary Isochromosomes

Complementary isochromosomes are rarely observed derivative chromosomes. They consist of two long or two short arms of a chromosome. As depicted in Fig. 2.4, their formation in connection with UPD is going together with a combination of rare events during meiosis and/or the first stages of zygote cell division.

Reported cases of complementary isochromosomes and UPD are listed in Table 2.4. The suggested mechanisms (Fig. 2.4), such as centromeric misdivision (Chen et al. 1999) or erroneous ‘trisomic’ rescue events (Albrecht et al. 2001), are speculative and have not been seen or mechanistically understood in real life yet (Hassold et al. 2007). However, some progress has been achieved in understanding the complex plasticity of the early embryo (Handyside et al. 2012).

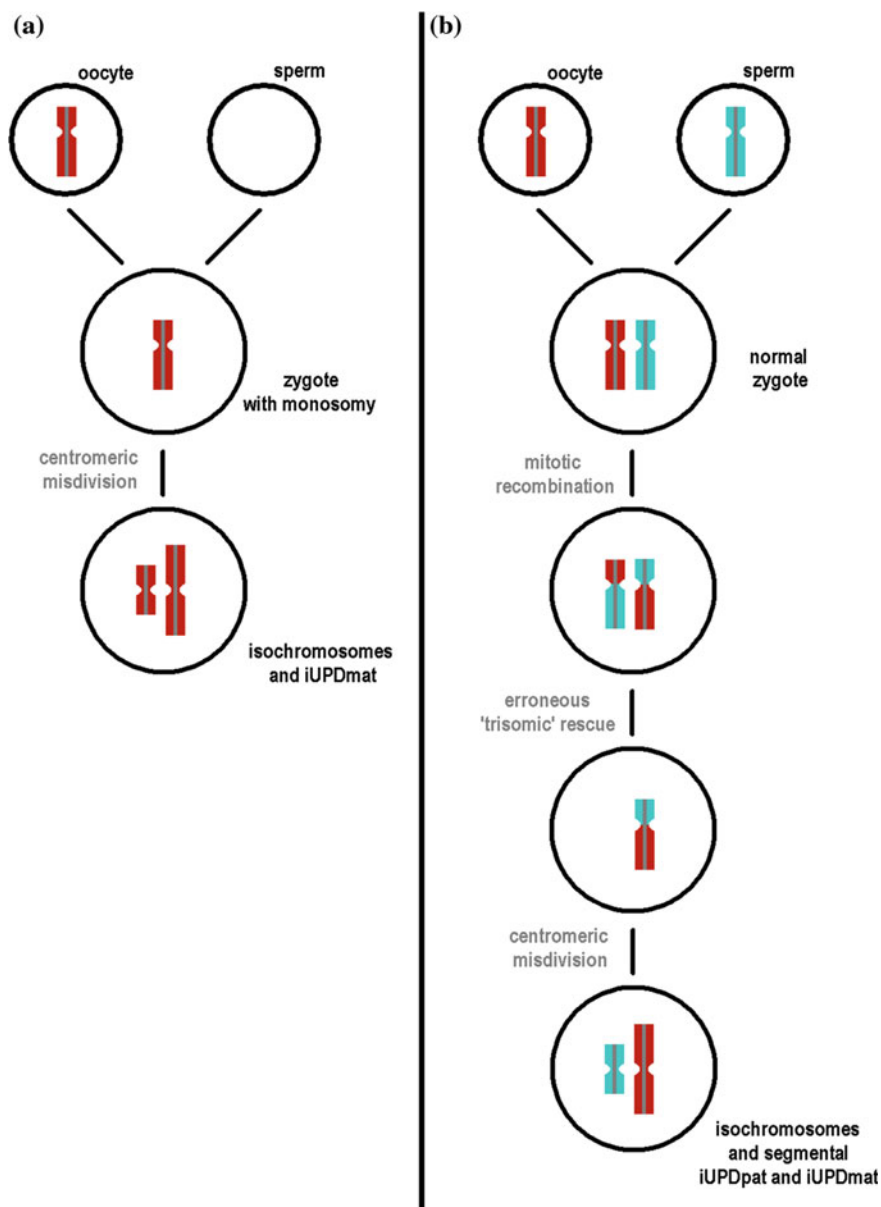


Fig. 2.4 **a** An isochromosome may be uniparental in origin and due to a centromeric misdivision in a monosomic zygote. **b** The isochromosome may be biparental in origin and the result of a normal zygote, which first performs a mitotic recombination in the centromere, followed by an erroneous 'trisomic' rescue event, and finally a centromeric misdivision as a monosomic rescue mechanism

Table 2.4 Complementary isochromosomes with UPD according to Liehr (2014c)

Case number	UPD type in p-arm	UPD type in q-arm
01-WpU-bal/1-1	UPD(1)pat	UPD(1)pat
02-OmU-bal/1-1	UPD(2)mat	UPD(2)mat
02-OmU-seg-q11/1-1	UPD(2)pat	UPD(2)mat
02-OpU-seg-pter/1-1		
02-OmU-seg-q11/1-2	UPD(2)pat	UPD(2)mat
02-OpU-seg-pter/1-2		
02-WmU-bal/2-1	UPD(2)mat	UPD(2)mat
04-OmU-bal/1-1	UPD(4)mat	UPD(4)mat
07-WmU-seg-q11/1-1	UPD(7)pat	UPD(7)mat
07-WpU-seg-pter/1-1		
07-WmU-seg-q11/1-2	UPD(7)pat	UPD(7)mat
07-WpU-seg-pter/1-2		
09-OmU-bal/1-1	UPD(9)mat	UPD(9)mat

2.2.3 Other Rearrangements

Apart from chromosomal heteromorphisms (Liehr 2014a), structural rearrangements, such as inversions, on both homologous chromosomes or isochromosomes transmitted through generations may be indicative of a UPD (Fig. 2.5).

Inversions have been reported for 46,XX,inv(3)(p12q24)x2 mat and 46,XX,inv(4)(p15.2q12)x2 mat, being indicative for maternal UPD of the corresponding chromosomes (Betz et al. 1974; Carpenter et al. 1982, Fig. 2.5a). Inversions are non deleterious for the carrier as long as they are balanced and none of the involved breakpoints is disrupting a gene. Problems may arise due to inversion loop formation during meiosis (Bhatt et al. 2014).

Chromosomal heteromorphisms as indicators of UPD have been reported only twice (Miyoshi et al. 2001; Ceylander et al. 2007, Fig. 2.5b). Such cytogenetically visible heteromorphisms lead to gain or loss of megabases of DNA. Because these heterochromatic DNA stretches do not contain any (relevant) genes, the heteromorphisms are considered to be balanced, rather than imbalanced, rearrangements.

Isochromosomes leading to no clinical problems are normally derived from acrocentric chromosomes (Kirkels et al. 1980; Palmer et al. 1980, Fig. 2.5c). They are cytogenetically indistinguishable from Robertsonian translocations (Sect. 2.2.1.1).

Overall, more cases should exist in which balanced chromosomal rearrangements occur with UPD. However, they might not have been identified because less than 50 % of UPD cases have been cytogenetically studied (Fig. 2.5) and chromosomal heteromorphisms were neither well analyzed nor reported in past decades (Liehr 2014a).

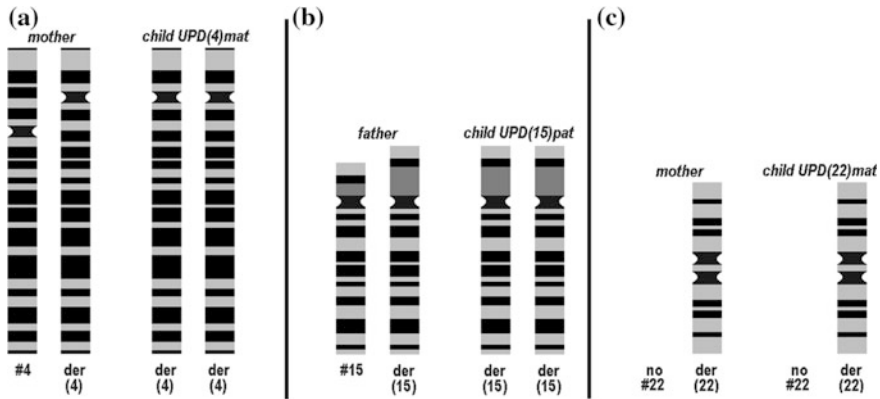


Fig. 2.5 In rare instances, derivative chromosomes may be indicative for iUPD presence. **a** Here, the mother had one $\text{inv}(4)(\text{p}15.2\text{q}12)$, the latter designated as $\text{der}(4)$ in the figure; she gave two copies of this $\text{der}(4)$ to her daughter, who thus had a maternal iUPD of chromosome 4. This case was reported by Carpenter et al. (1982). **b** The father had an eye-catching heteromorphism in 15p12 ($\text{der}(15)$) on one of his chromosomes 15. As the identical short arms of both chromosomes 15 were present in the offspring of this father and the mother did not have such heteromorphisms on her chromosomes 15, a paternal iUPD of chromosome 15 was diagnosed as AS, and reported by Ceylander et al. (2007). **c** An isochromosome 22 ($\text{der}(22)$) was present in a karyotype 45,XX,i(22)(q10). The mother gave the $\text{der}(22)$ to her daughter, who had the same karyotype and a maternal UPD of chromosome 22. Chromosomes drawn according to Kosyakova et al. (2009)

2.2.4 Segmental UPD in a Balanced Karyotype

In the case of isochromosome formation (Sect. 2.2.2), including homologous Robertsonian translocations (Sect. 2.2.1.1) and duplication of derivative chromosomes (Sect. 2.2.3), UPD should concern the entire derivative. Segmental UPD is present in all other balanced instances discussed previously, such as translocations and nonhomologous Robertsonian translocations.

Interestingly, not only the expected regions of such a derivative translocation chromosome must be exclusively affected by UPD. This is highlighted by a case with a karyotype 45,XY, $\text{der}(13;15)(\text{q}10;\text{q}10)$, UPD(15) pat, and AS: in this specific case; a segmental UPD(13) pat concerning 13q14.3 was also detected. A mitotic recombination event (Sect. 2.1.1) in early embryogenesis was suggested as the cause of this finding (Tsai et al. 2004).

2.3 Aberrant Unbalanced Karyotype

As outlined before, UPD may occur with a normal karyotype (Sect. 2.1) and an aberrant but balanced karyotype (Sect. 2.2). The third possibility is that UPD arises in connection with an unbalanced karyotype, with either gain (Sect. 2.3.1) or loss of genetic material (Sect. 2.3.2).

2.3.1 Gain of Genetic Material and UPD

Within a genome, a gain of genetic material may affect the whole chromosome set (Sect. 2.3.1.1), whole chromosomes (Sect. 2.3.1.2), or chromosomal parts (Sect. 2.3.2.2). Although segmental UPD plus a small genomic imbalance both may be present in all cells of a patient, trisomy or triploidy in combination with UPD can only arise in mosaic cases (see also Sect. 2.4).

2.3.1.1 Mosaic Triploidy

Triploid animals and plants have been described and are well known (Choleva and Janko 2013; Weiss-Schneeweiss et al. 2013). Complete triploidy in human is not compatible with life, even though triploidy is one of the most common chromosome abnormalities, occurring in 1–2 % of all conceptuses (Jacobs et al. 1982). In a triploid zygote, there may be two paternal plus one maternal (diandric) or one paternal plus two maternal (digynic) chromosome-sets. Survival time of such pregnancies is between 7 and 17 weeks of gestation (Hasegawa et al. 1997).

According to Daniel et al. (2003), “non-mosaic triploidy has a simple origin of either two sperm or a diploid sperm fertilizing a single ovum or a single sperm fertilizing a diploid egg or two fused haploid ova (retention of second polar body).” Diandric zygotes lead to complete hydatidiform mole. In this case, there is no embryo but “prominent extraembryonic tissues with atypical hyperplastic trophoblast and cavitated hydropic villi; digynic zygotes develop to ovarian teratomas, which is a constellation of well differentiated but disorganized mature tissues, usually including a dominant cyst lined by skin and associated with mesenchymal and endodermal derivatives. They are the most frequent type of ovarian tumor, representing 20 % of all ovarian tumors. Placental structures such as trophoblast are essentially never seen in mature teratomas of humans” (Mutter 1997).

Daniel et al. (2003) suggested the following three mechanisms for the origin of mosaic triploidy:

- (1) Chimaerism with karyotypes from two separate zygotes developing into a single individual
- (2) Delayed digyny, by incorporation of a pronucleus from a second polar body into one embryonic blastomere
- (3) Delayed dispermy, similarly by incorporation of a second sperm pronucleus into one embryonic blastomere

In 2009, additionally mosaic triploidy cases with UPD were reported. Therefore, the ideas from 2003 had to be adapted, as summarized in Fig. 2.6 (Morales et al. 2009).

Whole genomic UPD may also arise from nontriploid situations, as summarized in Fig. 2.7 (Morales et al. 2009). Parental genomes were shown to be always separated in healthy human tissues (Weise et al. 2013, Fig. 2.7c). Thus, replicative failure by erasing one haploid genome set became much more imaginable.

2.3.1.2 Mosaic Trisomy

Trisomy is considered to be the most predominant chromosomal aberration in human abortions (Fritz et al. 2001). Trisomy and monosomy (Sect. 2.3.2.1) may affect all human chromosomes during early embryogenesis (Handyside et al. 2012). Because the early embryo is able to correct numerical chromosomal aberrations (see also Sect. 2.3.1.1), mosaic trisomies, small supernumerary marker chromosomes (sSMC, Sect. 2.3.1.2.1), and/or UPD may be present in newborn children.

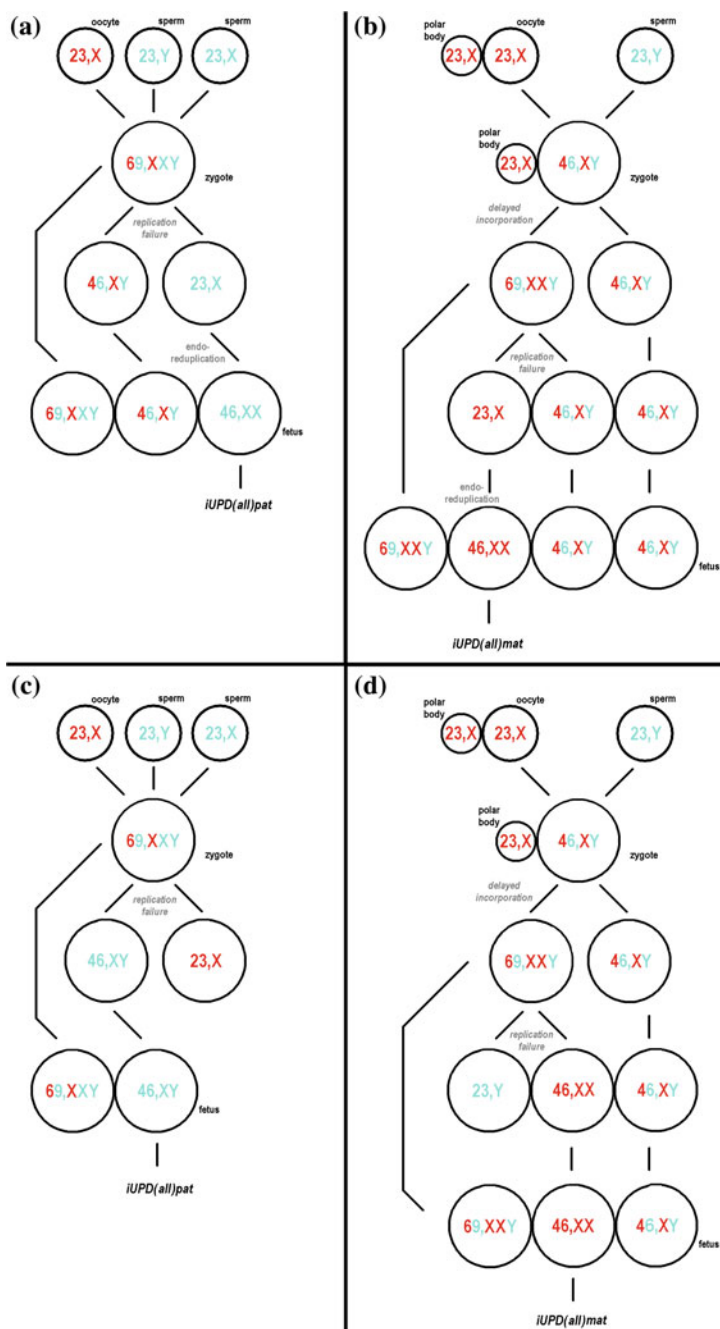
A relatively frequent finding is confined placental mosaicism due to initial trisomy followed by trisomic rescue, which is detected in 1–2 % of viable pregnancies (Robinson 2000). Confined placental mosaicism (CPM) characterizes a discrepancy between chromosomal findings in the chorion villi (i.e. placenta) sampling and in the fetus itself. For example, trisomy 21 may be detected in the placenta but a baby with a normal karyo- and phenotype is born. However, this baby may have tissues with mosaic karyotype $\text{mos } 47, \text{XN}, +21/46, \text{XN}$, and the cells with a numerically normal karyotype may have a UPD(21) (Fig. 2.8b).

Interestingly, in a small study, UPD was found in cases with CPM in which the chromosome abnormality was detected both in the cytotrophoblast and mesenchymal core (i.e., type 3 CPM) and not in such CPM cases limited to mesenchymal core (i.e., type 2 CPM; Toutain et al. 2010). In addition, postmeiotic errors may also lead to trisomy, later trisomic rescue, and UPD (Fig. 2.8c), sometimes in connection with a derivative chromosome (Fig. 2.8d).

Trisomic rescue can be the result of chromosome demolition of deliberate fragmentation and/or removal of one of the sets of three chromosomes during anaphase or metaphase. Such chromosome fragmentation is seen in Howell-Jolly bodies. A case with a $\text{del}(5)(\text{q}31)$ and one with a $\text{del}(8)(\text{q}21.1)$ (Varon et al. 2000) were interpreted as incomplete chromosome fragmentation (Fig. 2.9a; Liehr 2012):

Trisomic rescue (also may) consist of one correction event in the first to fourth postzygotic cell division with a subsequent unknown distribution of trisomic and disomic cells among the progenitor cells of the inner cell mass and trophoblast compartment until 16-cell stage (Fig. 2.9b). Cellular selection during the following formation of placenta and early embryogenesis would help, as a result, to ensure the presence of a numerically balanced chromosome complement in the developing fetus. (...) As aneusomies are more likely to be contributed from the female side, another kind of enzymatic content in male- and female-derived pronuclear compartments could also be important. The oocyte has a less active machinery to eliminate chromosomal mistakes than the spermatocyte. Thus, at the pronuclei stage, an elimination of a paternally derived additional chromosome could be more likely than that of a maternally derived one. In concordance with this, evidence for the existence of a chromosome counting mechanism in the zygote and early embryogenesis has been provided. Also, the recently discovered ‘chromosome kissing’ could be involved here (Liehr 2012).

Finally, a chromosome could be erased from a cell by some kind of micronucleus formation, as was shown in tumor cells (Ambros et al. 1997, Fig. 2.9c).



◀ **Fig. 2.6** The following models are provided to explain the finding of mosaic triploidy together with a numerically normal cell line and UPD of all 24 chromosomes. **a** A paternally derived whole genomic iUPD may be due to the fertilization of an oocyte by two sperm—in the example, one provides an X chromosome and one provides a Y chromosome. The triploid zygote undergoes a replicative failure leading to a normal male cell line and a haploid cell with karyotype 23,X (paternal). After genome endoreduplication, the fetal genome consists of three cell lines as depicted, including one female genome with UPD(all). Adapted from Morales et al. (2009). **b** A normal zygote is formed in this example, but a triploid cell is generated after the first cell division(s) due to delayed incorporation of the haploid genome of a polar body. A replication failure followed by endoreduplication leads to a mosaic fetus with a maternal iUPD. Adapted from Morales et al. (2009). **c-d** As in the previous models, replicative failure leads to a numerically normal cell line with UPD(all); this cell line can now build different kinds of mosaics

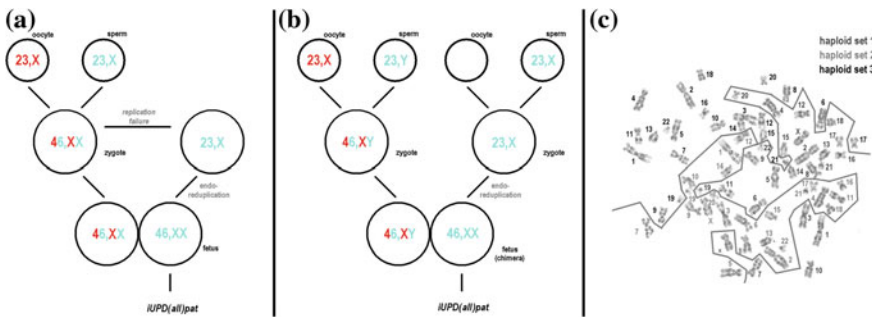


Fig. 2.7 **a** Genome-wide UPD may also arise due to replicative failure from a normal zygote. Endoreduplication leads then to a female with mosaic paternal iUPD or maternal iUPD (not shown). Adapted from Morales et al. (2009). **b** A chimera may form a mosaic i(UPD) paternal or maternal (not shown). Adapted from Morales et al. (2009). **c** Triploid metaphase spread 69,XXX can be easily divided into the three conserved regions of each of the three underlying haploid chromosome sets

Trisomic rescue has been observed together with mosaicism and UPD for many chromosomes (Fig. 2.10). No mosaic trisomy has been seen in chromosomes 1, 3, 5, 8, 13, 18, and 19; however, trisomy for these chromosomes in early embryogenesis is possible (Handyside et al. 2012). Almost 50 % of all reported UPD cases with mosaic trisomy are derived from chromosome 16. The reason for this correlation is not yet known.

Interestingly, 10 cases of UPD with gonosomal trisomy have been reported: six cases with a karyotype 47,XXX and a UPD(6), UPD(14), or UPD(15) and also four 47,XXY cases with a UPD(6), UPD(15), or UPD(16). In addition, there is one case with a UPD(16) and mosaic trisomy 8 and 16 and another one with UPD(21) combined with trisomy 7 and 9 (Liehr 2014c). At present, it is unclear if these findings indicate specific modes of UPD formation or are just chance findings.

Mosaic trisomy of the placenta and/or the fetus can obviously lead to clinical problems. Mosaic trisomy normally is correlated prenatally with intrauterine growth retardation and increased risk for abortion, especially if trisomy is

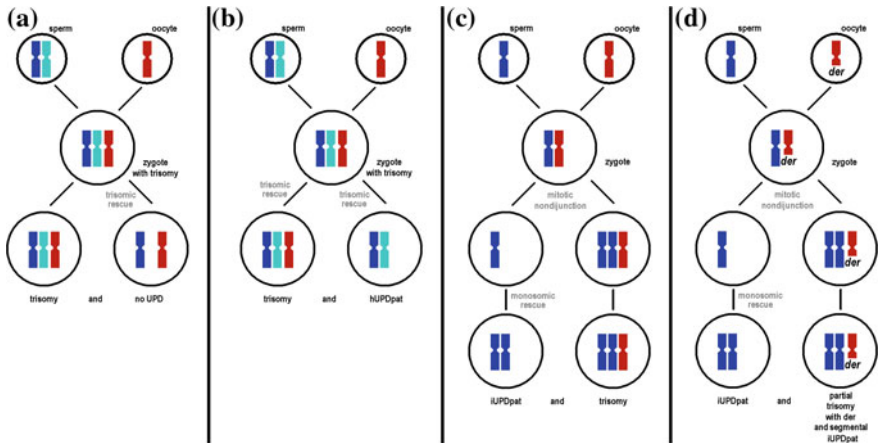


Fig. 2.8 Different ways that UPD can form in connection with a (mosaic) trisomy are shown. **a** Trisomy may form due to a disomy in a sperm or an oocyte (not shown). The zygote is trisomic. Later, during cell divisions, trisomic rescue happens. In the case shown here, no UPD but normal disomy is the result. **b** Here, the same situation as in Fig. 2.8a) is shown. After trisomic rescue, a hUPDpat is the result in the disomic cells. **c** Sperm and oocytes are monosomic, whereas the zygote is disomic. Due to a mitotic nondisjunction, a trisomic cell and a monosomic cell form; the latter becomes disomic by monosomic rescue and has a iUPDpat. **d** The sperm has a normal chromosome complement. The oocyte provides a partial nullisomy due to a derivative chromosome (der). The zygote has a partial monosomy. Due to mitotic nondisjunction, a monosomic and a partial trisomic cell line develops. The monosomic one is rescued by duplication of the remainder chromosome. In the end, both cell lines have complete or partial iUPDpat

expressed in the placenta (Ledbetter and Engel 1995). In UPD cases, the effects of trisomy may be mixed up with putative imprinting defects, as reported for chromosome 2 (Ledbetter and Engel 1995) and chromosome 16 (Yamazawa et al. 2010). Intrauterine growth retardation may be due to trisomy rather than UPD, as confirmed by a study summarizing more than 150 corresponding cases (Kotzot et al. 2000).

The incidence of meiotic nondisjunction has been observed to increase with advanced maternal age. Thus, because UPD is a result of trisomy followed by trisomic rescue in ~60 % of the cases (Fig. 2.7), it is not surprising that UPD mat is seen more often in the offspring of mothers with advanced maternal age (Ginsburg et al. 2000; Schinzel 2001; Yoon et al. 2013; see Sect. 3.3). Besides enhanced rates of nondisjunction in meiosis 1 of older oocytes, reduced recombination rates between homologous chromosomes may also be present there; an increased frequency of achiasmate tetrads has been suggested (Robinson et al. 1998). Handyside et al. (2012) suggested that failure of cohesion in oocytes from women with advanced maternal age is a possible reason for reduced numbers or altered distribution of recombination events. If homolog chromosomes fail to crossover, this would be expected to produce random segregation at meiosis I and,

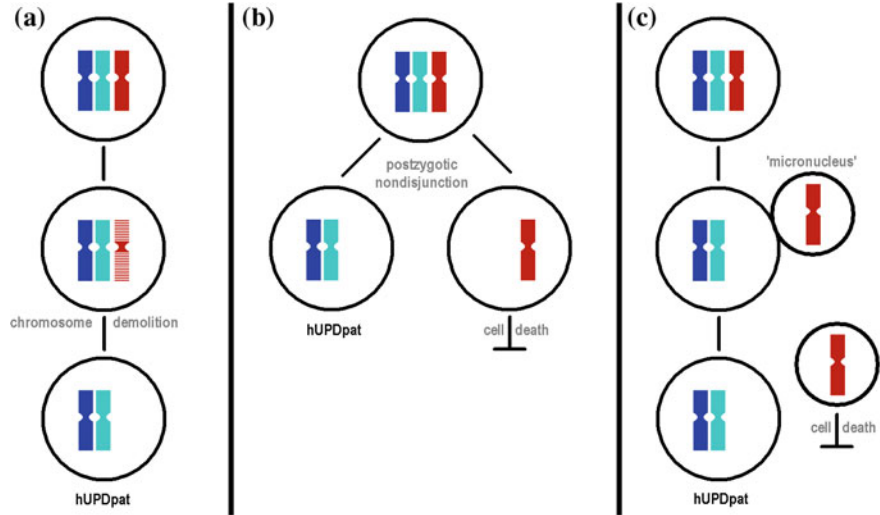


Fig. 2.9 Ideas how trisomic rescue could work are shown. Only situations are shown in which hUPDpat arise; iUPD is also possible in the same ways if the male sperm had a corresponding meiosis II error. **a** Chromosome demolition: one supernumerary chromosome is selected and demolished by unknown mechanisms. **b** Postzygotic nondisjunction: the trisomic cell divides into a disomic and monosomic one. The monosomic is lost and not rescued by monosomic rescue. **c** Micronucleus formation: one supernumerary chromosome is selected and unloaded from the cell by unknown mechanisms

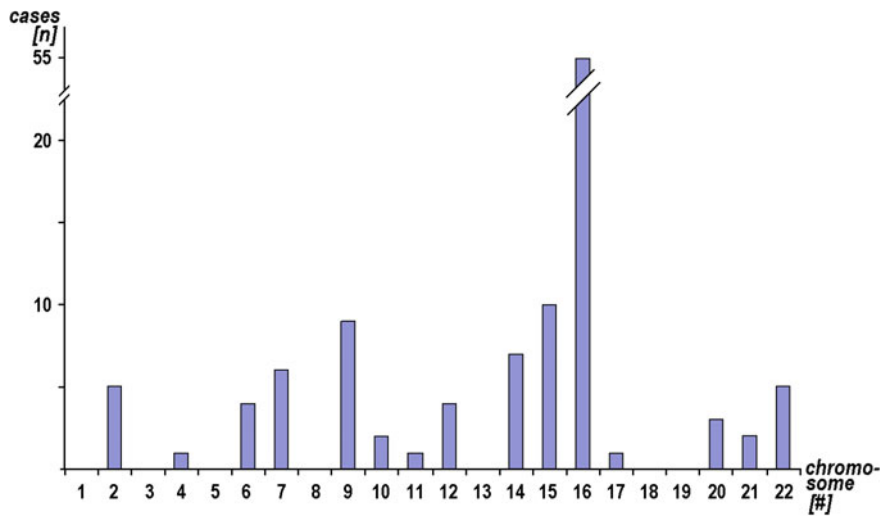


Fig. 2.10 Chromosomal distribution of mosaic trisomy with corresponding autosomal UPD is depicted, according to Liehr (2014c)

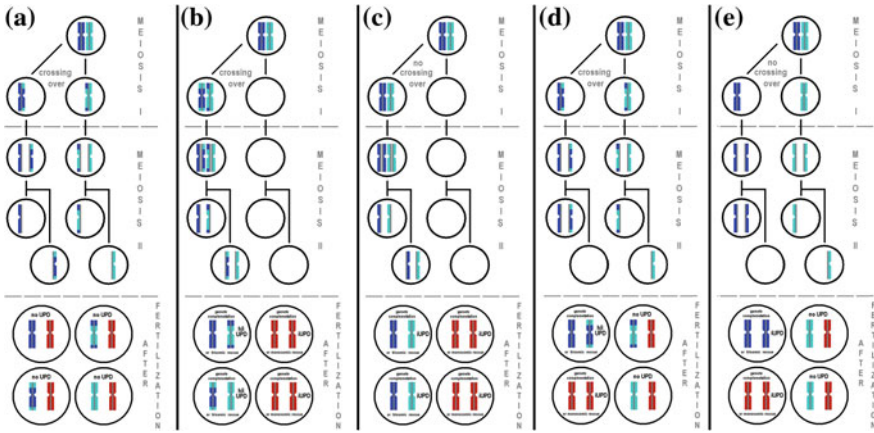


Fig. 2.11 Different variants of male meiosis are depicted. In the upper part of all five parts of this figure (a–d), meiosis I and II are shown; the *lower parts* depict the situation after fertilization. **a** Male meiosis without any nondisjunction errors leads only to zygotes without UPD. **b** A meiosis I nondisjunction leads to two disomic and two nullisomic sperm. If those sperm variants fertilize a monosomic oocyte, trisomy or monosomy (not depicted) results. If trisomic or monosomic rescue happens in the numerically abnormal zygotes, the four situations depicted here may be the result, either hUPDpat or iUPDmat. If the disomic sperm meets a nullisomic gamete, gamete complementation and hUPDpat will be the consequence. If the nullisomic sperm meets a monosomic oocyte, this cell can rescue itself by monosomic doubling of the sole maternal chromosome; thus, iUPDmat is the outcome. If the nullisomic sperm fertilizes a disomic oocyte, either iUPDmat (shown) or hUPDmat (not shown) can be the result. **c** The same situation as in Fig. 2.11b, but no crossing-over takes place. Thus, if a pregnancy occurs, only iUPD can result. **d** A meiosis II error leads after fertilization to two zygotes without UPD, one with monosomy and one with trisomy. The trisomic zygote, if it is getting rid of the maternal chromosome copy, may be transformed to a disomic cell with iUPDpat. The monosomic zygote may perform monosomic rescue leading to iUPDmat. As described in Fig. 2.8b, in the case of gamete complementation, iUPDmat or hUPDmat (not shown) may be the result. **e** The same situation as in Fig. 2.11d, but no crossing-over takes place. Thus, if a pregnancy occurs, only iUPD can be the result after trisomic rescue or gamete complementation

“consequently, a 50 % chance of non-disjunction. However, for certain chromosomes the situation is more complicated, with unusual locations of crossovers being correlated with non-disjunction” (Hassold et al. 2007, Fig. 2.11).

Unlike that mentioned for women, no age association was found for UPDpat (Ginsburg et al. 2000; Schinzel 2001; Yoon et al. 2013, see Sect. 3.3).

Chromosomes occupy special regions within the interphase nucleus (Manvelyan et al. 2008). This may be the reason for the finding that different trisomies form preferentially at different stages of meiosis. This speculation is substantiated Table 2.5. Chromosomes 15 and 16, which acquire trisomy preferentially due to a nondisjunction in meiosis I, have a central position. However, chromosome 18, which as a peripheral positioning, becomes trisomic by a meiosis II error.

Table 2.5 Potential correlation of chromosome positioning (Manvelyan et al. 2008) and data for the preferential origin of trisomy due to meiosis I or II error (Engel 2006)

Chromosome	Position in nucleus	Meiosis I error → trisomy	Meiosis II error → trisomy
15	central	+	
16	central	+	
18	peripheral		+

Single Small Supernumerary Marker Chromosomes

Single small supernumerary marker chromosomes (sSMCs) are present in approximately 3 million of the 7 billion human beings alive. sSMCs can be inverted duplication shaped, ring shaped, or centric minute shaped (Fig. 2.12). As reviewed in Liehr et al. (2011a), all three shapes can be found in combination with UPD. Interestingly, only de novo sSMC have been found to be associated with UPD, not parentally inherited ones; an exception are the complex sSMCs (see below). Figure 2.12 depicts some possibilities of how UPD together with sSMC may form. It has only been shown for centric minute-shaped sSMCs that a trisomy must have been present initially. Bartels et al. (2003) found a centric minute-shaped sSMC derived from chromosome 22 in prenatal diagnostics; the placenta had a karyotype mos 47,XX,+22/46,XX (Fig. 2.12a).

For ring-shaped sSMCs exclusively, the McClintock mechanism was repeatedly seen in sSMC; however, no UPD has been associated with it yet. For all other sSMCs of that shape, either no explanation for their formation was offered or case-specific unique complex rearrangements were suggested. The McClintock mechanism describes a break within or near the centromere together with a break in the other arm, creating finally a small ring and an acentric fragment (Fig. 2.12b).

Inverted duplication-shaped sSMCs are thought to form by intra- or inter-chromosomal U-type exchange (Fig. 2.12c; Liehr 2012). sSMCs and UPD can also theoretically arise due to gametogenesis mistakes (Fig. 2.12d).

Complex sSMCs are small extra chromosomes that derived from more than one chromosome. Normally, they result from a balanced translocation in one parent. The most prominent example is derivative chromosome 22 syndrome, also called Emanuel syndrome, but more than 100 other examples of complex sSMCs have been reported (Liehr et al. 2013). UPD has rarely been tested; however, segmental UPD must be suggested to be present in all these cases (Fig. 2.13).

Multiple and Neocentric sSMCs

For multiple sSMCs (Liehr et al. 2006; Liehr 2012) and their formation, only one suggestion has been published to date. Daniel and Malafiej proposed in 2003 that sSMC are derived from transfection of a chromosome or its fragments into the zygote, which are derived from a superfluous haploid pronucleus that is usually

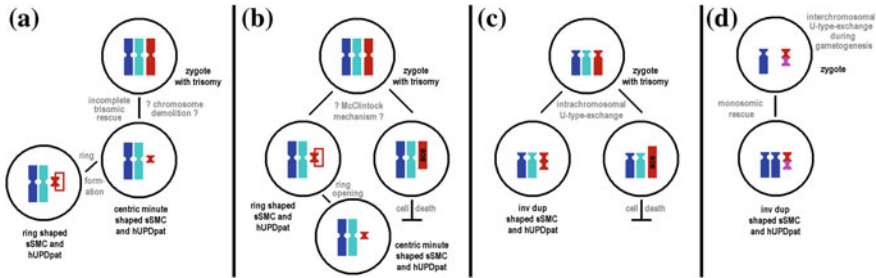


Fig. 2.12 UPD may go together with sSMC formation. Here, possible modes of formation starting from a trisomy are depicted. Besides UPDpat (shown), sSMC formation also may lead to UPDmat or no UPD (not shown). **a** Trisomic rescue by chromosome demolition (Fig. 2.9a) may lead to a centric minute-shaped sSMC. Sometimes, centric minute-shaped sSMCs also go together with a mosaic in which the same sSMC has a ring shape. One possibility how this may form is shown here; for another, see Fig. 2.12b. **b** Ring-shaped sSMCs may form by the McClintock mechanism. The ring-shaped sSMC remains stable in the cells of the fetus, while the acentric fragment (ace) either is taken to the sister cell, which goes to apoptosis, or remains in the same cell with the sSMC but is degraded (this possibility is not depicted here). As mentioned in Fig. 2.12a, mosaic cases having centric minute- and ring-shaped sSMCs exist together; they also might form by ring opening. **c** Inverted duplication-shaped sSMC can form due to mitotic intrachromosomal crossing-over. The acentric fragment may behave as described in Fig. 2.12c. **d** Interchromosomal crossing-over leading to an inverted duplication-shaped sSMC should only be possible due to a U-type exchange in gametogenesis. In addition, intrachromosomal crossing-over can also appear during this stage of development

degraded by deoxyribonucleases or other means. Unfortunately, multiple sSMC are hardly ever studied for UPD; in those few cases that were studied, no UPD was discovered. Still, UPD may also arise there, possibly due to the rescue of multiple trisomies, such as in cases with segmental UPD(9) and mosaic double trisomy of chromosomes 9 and 22 (Rodríguez-Santiago et al. 2010).

Principally, it should also be possible for UPD to occur with neocentric sSMC, where no UPD was reported yet (Klein et al. 2012). In the case of UPD and a neocentric inverted duplication sSMCs would be found, this finding would also support the idea that U-type exchange and UPD formation have a connection (Fig. 2.12c).

Unbalanced Translocations and Duplications

Together with loss of copy numbers and segmental UPD, gain may arise due to or in connection with unbalanced translocations or inversion loop formation. Apart from that, pure partial duplications also may lead to segmental UPD, although rarely. The reported cases are summarized in Table 2.6.

Complex sSMCs are another example of pure gain of chromosomal material plus UPD (Sect. 2.3.1.2.1, Fig. 2.13).

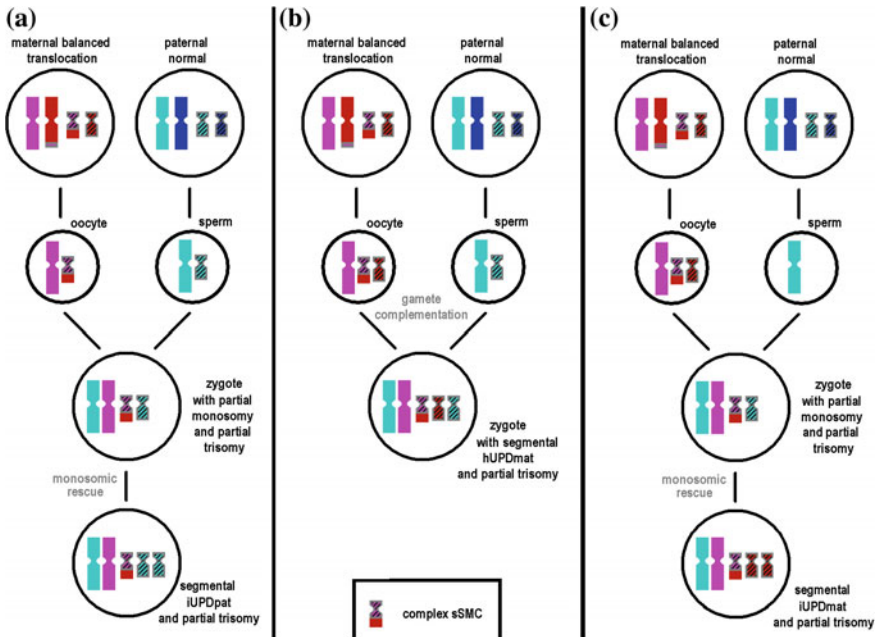


Fig. 2.13 Complex sSMCs result in many cases from a balanced parental translocation event. Here, an example with a maternal balanced translocation of a non acrocentric and an acrocentric chromosome is depicted, such as chromosomes 11 and 22 in Emanuel syndrome. Because only unbalanced offspring with the small derivative chromosome is viable, only this situation is depicted. The complex sSMC scheme is highlighted in the lower central part of the figure. **a** The complex sSMC (acrocentric derivative chromosome) is going to the oocyte instead of the normal sister chromosome. Thus, after fertilization, only monosomic rescue of the normal paternal acrocentric chromosome leads to a viable fetus. This includes iUPDpat and partial trisomy of the acrocentric and the non acrocentric chromosome. **b** If complex sSMC and a normal acrocentric chromosome go into the oocyte and fertilization with a normal sperm happens, a viable zygote with iUPDmat and partial trisomy of the acrocentric and the non acrocentric chromosome result. **c** In the case of gamete complementation, partial iUPDmat and partial trisomy of the acrocentric and the non acrocentric chromosome would be the result

2.3.2 Loss of Genetic Material and UPD

As stated for the gain of genetic material and UPD (Sect. 2.3.2), whole genome loss and whole or partial chromosome loss is possible in principle. Haploid chromosome sets in humans are only viable as sperm or oocytes. Whole chromosome loss in humans is only viable as monosomy X (Turner syndrome). However, monosomy can be repaired by duplication of the remainder chromosome, leading to iUPD (Sect. 2.3.2.1). Also, nullisomy can be present and can lead to hUPD by gamete complementation (Sect. 2.3.2.2). Finally, UPD can occur with unbalanced translocations and deletions (Sect. 2.3.2.3).

Table 2.6 Cases with UPD occurring with unbalanced translocations, pure duplications, or pure deletions

Chromosome	UPD plus imbalance	Case number
<i>Unbalanced translocations</i>		
11	46,XY,der(15)t(11;15)(p15.5;p12)mat	11-WmU-imb/1-1
11	mos 46,XX,der(19)t(11;19)(q13;p13.3)/46,XX	11-WmU-seg-q13/1-1
15	45,XY,der(5)t(5;15)(q35;q13)pat,-15	15-WmU-imb/5-1
16	mos 46,XY,der(1)t(1;16)(p36.6;p13.1)/46,XY	16-WmU-imb/4-1
20	mos 47,XX, +20/45,XY,psu dic(20;20)(p13;p13)/ 46,XX,psu dic(20;20)	20-WpU-imb/1-1
<i>Inversion loop formation</i>		
18	46,XX,rec(18)dup(p)inv(18)(p11.31q21.33)mat, rec(18)dup(q)inv(18)(p11.31q21.33)pat	18-WmU-seg-pter/2-1, 18-WpU-seg-pter/1-1
<i>Duplications</i>		
1/7	aCGH: dup(1)(p35.2-p32.2)[74 %],dup(1)(pter-p35.2) [55 %],dup(7)(q11.22-qter) [48 %]	01-OU-seg-pter/1-1, 07-OU-seg-q11.22/1-1
8	46,XY,dup(8)(pter → p23.3::p12 → p23.3::p23.3 → qter)	08-WpU-seg-p23.3/1-1
<i>Deletions</i>		
7	45,XY,psu dic(7;7)(p22;p22)	07-WpU-imb/1-1
8	45,XX,-8,psu dic(8)(p23.3)	08-WmU-imb/1-1
8	45,XX,-8,psu dic(8;8)(p23.1;p23.3)	08-WmU-imb/2-1
11	46,XY,del(11)(q23.3)/46,XY	11-WmU-seg-q23.3/1-1
22	46,XX,del(22)(q13.2)[73]/46,XX[27]	22-WpU-seg/1-1
<i>Deletions and no (obvious) connection to detected UPD</i>		
8	aCGH: del(15)(q13.3q14)	08-WpU-N/3-1
15	46,XN,del(11)(q21q22.3)	15-WpU-imb/1-1

2.3.2.1 Monosomic Rescue and UPD

Autosomal monosomies are rarely reported as reasons for human abortions. However, studies in preimplantation embryos showed that monosomies are as frequent as trisomies (Fritz et al. 2001). Paternal UPD is most often iUPD, most likely due to monosomic rescue (Papenhausen et al. 2011). Monosomic rescue can be present in connection with UPD formation and Robertsonian translocations (Fig. 2.3), mitotic nondisjunction (Figs. 2.8 and 2.13a, Bartsch et al. 1994), and different meiosis errors, as depicted in Figs. 2.11 and 2.12d.

In humans, only monosomy X is viable. Therefore, it would not be surprising to also find coincidences of a 45,X karyotype and a UPD, although only one such mosaic case with UPD(14)mat has been reported (Mitter et al. 2006).

2.3.2.2 Gamete Complementation

Gamete complementation is based on fusion of a nullisomic and a disomic gamete, resulting in UPD. The chance for this is estimated to be less than 1 in 1,000,000

cases (Shaffer et al. 2001) and 1 in 5,000 births (Robinson 2000). Cases due to gamete complementation were reported repeatedly (e.g. Wang et al. 1991; Cotter et al. 1997; Park et al. 1998; Berend et al. 1999). However, as discussed in [Sect. 2.5](#), it is unclear if these cases can also be explained by other mechanisms outlined in this chapter.

2.3.2.3 Unbalanced Translocations and Deletions

Unbalanced translocations leading to loss plus gain of genetic material and UPD have already been discussed ([Sect. 2.3.1.2](#), [Table 2.6](#)). In addition, there are a few more cases ([Table 2.6](#)) with deletions due to translocations between homologous chromosomes with partial nullisomies and mosaic cases with partial chromosomal deletions (monosomies). In the latter cases, the UPD was most likely induced by the mechanism depicted in [Fig. 2.8](#). Interestingly, there are also a few cases with partial deletions without any (obvious) context to the observed UPD ([Table 2.6](#)), which may indicate more complex previous chromosomal rearrangements in those cases.

Finally, a UPD-like effect may arise if an imprinted chromosomal region is deleted. In that case, there remains only one (e.g. maternal) copy of a gene region, having an identical effect as two copies of the maternal chromosomes. This is one major mechanism of PWS ([Sect. 4.6](#)).

2.3.2.4 Segmental UPD and Aberrant Unbalanced Karyotypes

The chromosomal segments involved in segmental UPD formation may be terminal or interstitial. As mentioned previously, they can result from inherited, meiotic, or somatic crossing-over events ([Figs. 2.2, 2.4 and 2.13](#)).

2.4 UPD and Mosaicism

If UPD is present in mosaic (with or without a cytogenetically visible chromosomal aberration), postfertilization errors should be considered as a cause of its formation (Yamazawa et al. 2010). Such events may happen early in embryonic development and lead to whole chromosome iUPD by replacement of an abnormal chromosome (Bartsch et al. 1994; Miyoshi et al. 1999) or later in life confined to one tissue or organ (Tuna et al. 2009). In BWS, mosaicism of UPD(11) pat is the norm rather than the exception (Slatter et al. 1994).

Table 2.7 Possible conclusions on UPD formation from the molecular and/or cytogenetic result

	Meiosis error	Trisomic rescue	Monosomic rescue	Mitotic nondisjunction	Gamete complementation	Postfertilization error
hUPD	+	+	—	—	+	+
hUPD/iUPD	+	+	—	—	+	+
h/iUPD	+(meiosis I)	+	—	(—)	+	+
iUPD distal						
h/iUPD	+(meiosis II)	+	—	(—)	+	+
iUPD proximal						
iUPD	+	+(crossing over defect)	+	+	+	+
Trisomy mosaic	+	+	+	+	+	+
Other mosaic	+	+	+	+	+	+

2.5 Which Type of Formation Should be Considered?

In this chapter, it becomes clear that UPD is almost always based on chromosomal rearrangements. Jointly considering information on UPD, derivative chromosomes, and mosaics provides unique insights, making otherwise impossible mechanisms in gameto- and early embryogenesis seem feasible. The possibilities of the cell to detect, repair, and compensate for chromosomal imbalances and defects are amazing. This ability seems to be especially expressed in pluripotent cells (Bershteyn et al. 2014).

Beginning from that point, it seems almost impossible to unequivocally deduce the phase in which an error leading to UPD appeared in each case. In Table 2.7, different UPD constellations and possible modes of formation are aligned. As in UPD cases, many unlikely things must happen together, nearly every mode (or not less than two modes) of formation can be suggested for each of them. An example of this dilemma was reported in 2001.

Uniparental Disomy (UPD) in Clinical Genetics

A Guide for Clinicians and Patients

Liehr, Th.

2014, XVIII, 192 p. 36 illus., 26 illus. in color., Hardcover

ISBN: 978-3-642-55287-8