Uniparental disomy (UPD) is defined as the inheritance of both homologues of a chromosome pair from only one parent and no copy from the second parent in a diploid genome (1). UPD is classified as maternal or paternal, depending on the origin of the disomic chromosome. UPD can be further classified as uniparental heterodisomy (hUPD) or uniparental isodisomy (iUPD). The two inherited chromosomes in full iUPD represent two copies of a single parental chromosome, whereas the two inherited chromosomes in full hUPD represent both chromosomes of a sole parental donor. Segmental UPD for a region of both chromosomes of a pair, with biparental inheritance for the rest of the chromosome pair and a normal karyotype can also occur (2).

UPD is rare, as it generally requires two independent chromosome non-disjunction events. In the first event, UPD results from the failure of the two members of a homologous chromosome pair to segregate properly into two daughter cells during meiosis I (MI) or II (MII). The...
resulting gametes contain either both (disomic) or no (nullisomic) copies of the chromosome, instead of the normal single copy of each chromosome (haploid). This leads to a conception with either three copies (trisomy) or one copy (monosomy) of the chromosome. In order to rescue the conceptus to disomy, a second event must occur. The second event results in the loss of the extra chromosome in the trisomy (trisomy rescue) or the duplication of the single chromosome in the monosomy (monosomy rescue). Theoretically, of the three chromosomes in the trisomy, the ‘lost’ chromosome will originate from the normal haploid gamete one third of the time, thus resulting in UPD one third of the time. Similarly, trisomy involving a Robertsonian translocation or a 3:1 interchange trisomy can also resolve into disomy by loss of the chromosome from the normal haploid gamete, resulting in UPD (2, 3).

UPD can also occur by other rare mechanisms. Examples include gamete complementation, in which a gamete, by chance, is disomic for the same nullisomic chromosome of the second gamete (4); post-fertilization error (by somatic recombination or gene conversion), resulting in segmental UPD (2, 4); somatic replacement of a derivative chromosome (5); correction of interchange monosomy, isochromosome formation (including complementary isochromosomes), and correction of a trisomy resulting in a supernumerary, extra structurally abnormal chromosome (ESAC) in which there is UPD for the same chromosome from which the ESAC was derived (2, 4, 6, 7). For example, chromosome 15 ESACs comprised entirely of heterochromatin have been associated with UPD15 and probably represent the remnants of a trisomy rescue (8).

The majority of non-disjunction occurs in maternal meiosis I (MI) (9). This will result in 50% disomic and 50% nullisomic ova. Fertilization of the disomic ovum by a normal haploid sperm will result in a trisomic conceptus. Therefore, it is more likely for a trisomy to consist of two maternal chromosomes and one paternal chromosome. Theoretically, one third of the time, trisomy rescue will thus result in maternal hUPD from an MI nondisjunction and any regions of isodisomy probably reflect meiotic recombination. Autosomal monosomies are generally lethal early in embryogenesis. The rescue of a monosomic conceptus following fertilization of a nullisomic ovum with a normal haploid sperm can occur by post-zygotic duplication of the single paternal chromosome, either as a duplicate ‘free’ chromosome or usually resulting in isochromosome formation, with obligatory paternal iUPD (10).

UPD for the majority of chromosomes is without phenotypic effect (11). The clinical consequences associated with UPD are fourfold (11). First, UPD for a few chromosome segments can result in clinically recognizable developmental abnormalities as a result of imprinting effects through parent-of-origin differences in gene expression. Second, the presence of homozygosity in iUPD, representing duplicate copies of a single parental autosomal chromosome, may result in two copies of an autosomal recessive mutation from the heterozygous carrier parent with the consequent recessive genetic disorder in the child. Third, the presence of homozygosity in iUPD of the X chromosome, representing duplicate copies of a single X chromosome, can result in recessive X-chromosomally inherited disorders in women. Paternal UPD XY can also result in father–son transmission of X-linked disorders. Fourth, UPD resulting from trisomy rescue is often associated with placental or foetal mosaicism. In this case, the specific clinical effects of the UPD are difficult to isolate from those of mosaic trisomy.

**Clinically significant UPD phenotypes**

Genomic imprinting is defined as the differential expression of a gene(s), depending on the sex of the transmitting parent. It is estimated that approximately 100 genes are imprinted (3) and, because these genes are almost always clustered, there are fewer imprinted chromosome regions (3). Thus far, only five chromosomes have been defined as imprinted based on the associated clinical phenotypes and synteny with mouse chromosomes (3): chromosomes 6, 7, 11, 14, and 15.

Paternal UPD6 has been reported in approximately 20% of cases with transient neonatal diabetes mellitus (DMTN) (5), which is generally associated with intrauterine growth retardation (IUGR) and macroglossia (3). DMTN usually resolves by 6 months of age. The majority of cases have a normal chromosome complement. DMTN is treatable and diabetes mellitus type II, which may appear later in life, is a common and treatable disorder in western populations (12).

Maternal UPD7 has been identified in approximately 5% of patients with Silver-Russell Syndrome (SRS), characterized by prenatal and postnatal growth retardation, retarded bone age, triangular facies and other dysmorphic features, and sometimes limb and facial asymmetry. Mild developmental delay has been reported in approximately one-half of cases. The majority of cases have a normal chromosome complement (3, 5). The outcome of children with maternal UPD7 is
not well defined, as the number of cases is small. However, a good outcome has been reported in cases with a positive family environment and treatment with growth hormone therapy (13). Reports of maternal UPD7 and poor outcome are associated with additional complications, such as trisomy 7 mosaicism (13).

Segmental paternal iUPD of 11p15 has been identified in approximately 20% of patients with Beckwith-Wiedmann syndrome (BWS), an overgrowth syndrome characterized by macroglossia, organomegaly, omphalocele, and an increased risk for embryonal tumours (3, 5). The segmental iUPD of 11p15 indicates that the UPD in BWS is as a result of a post-fertilization error (by somatic recombination or gene conversion). Mosaic full paternal UPD11 has been associated with severe IUGR (14) and a single case of mosaic full paternal UPD11 has been seen with typical BWS (15). Mosaic segmental maternal UPD11 for 11q13->qter has been reported in a single case complicated by mosaic trisomy of the same chromosome segment (16). In addition, chromosome 11p15 abnormalities involving methylation defects and maternal duplications have been reported in approximately 40% (17) to 64% (18, 19) of SRS patients. Mosaic, full maternal UPD11 has also been reported in a patient with SRS (20).

Maternal UPD14 results in individuals with short stature, hypotonia, precocious puberty, postpubertal truncal obesity, and small hands and feet. Paternal UPD14 shows a more severe phenotype, with mental retardation, polyhydramnios, IUGR, cardiomyopathy, skeletal abnormalities that result in short-limb dwarfism with narrow thorax (‘coat-hanger’ sign), and dysmorphic facies. UPD14 has been reported in association with Robertsonian translocations, mosaicism, isochromosomes, and ESACs involving chromosome 15 (3, 5–7).

UPD phenotypes of uncertain clinical significance

There have been some reports that chromosomes 2, 16, and 20 may also have imprinted regions. However, the data for these chromosomes are few and clinical phenotypes are complicated by developmental consequences associated with the presence of trisomic cells in the placenta and/or foetus (3, 5, 24–27).

Indications for postnatal UPD testing

Postnatal UPD testing is carried out to provide a diagnosis and thus facilitate appropriate patient care, as well as to inform the parents of prognosis and recurrence risk.

Postnatal UPD testing is recommended for:

1. individuals who present with multiple congenital anomalies, developmental delay/mental retardation and who have either:
   - a balanced Robertsonian translocation involving chromosome 14 or 15 (both familial and de novo);
   - a supernumerary marker chromosome derived from chromosome 14 or 15 and containing no apparent euchromatic material, but which may be indicative of a trisomy rescue event;

2. newborns with neonatal diabetes mellitus;

3. patients with clinical features suggestive of maternal or paternal UPD14;

4. patients found to be homozygous for an autosomal recessive disease causing mutation and only one parent is a carrier for that mutation, assuming that other potential explanations such as non-paternity, heterozygous deletion, testing artifact, etc. have been excluded; and

5. women found to be homozygous or apparent father–son transmission for an X-linked disorder.

Postnatal UPD testing should be considered in individuals who present with multiple congenital anomalies, developmental delay/mental retardation
and who have a non-Robertsonian translocation between any chromosomes known to carry imprinted genes. Despite the fact that familial non-Robertsonian translocations should, theoretically, also lead to an increased risk of UPD, to date only a few cases have been reported in the literature (28–30). Because the association between UPD and reciprocal translocation may exist with an under-estimated frequency, UPD testing should still be considered (31).

For the situations listed below, UPD is only one of the mechanisms causing the disorder and may not be the most common. Each centre should have its own testing algorithm for the following disorders:

1. SRS and a normal karyotype;
2. BWS and a normal karyotype; and
3. PWS/AS and an abnormal methylation pattern, where a deletion involving the critical region has been ruled out.

Indications for prenatal UPD testing

Prenatal UPD testing is carried out to provide a diagnosis in clinical situations at increased risk for an imprinting disorder. Testing should be carried out in a timely manner because of the limited time available for decision making.

Prenatal testing is recommended in foetuses with:

1. a balanced Robertsonian translocation involving a chromosome 14 or 15 or isochromosome (both familial and de novo), or a de novo ESAC with no apparent euchromatic material (32);
2. a normal karyotype when the parent is a carrier of a balanced Robertsonian translocation of chromosomes 14 and/or 15 (see text below for a case study);
3. level II or level III (see following text) amniotic fluid mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, or 15; and
4. level II or level III (see following text) chorionic villus sample (CVS) mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, or 15.

Based on the literature, it has been generally accepted that a normal karyotype in a foetus with a parent who is the carrier of a balanced Robertsonian translocation does not indicate a significant risk for UPD (see point 2 above), although studies to date are of too small sample size to achieve statistical significance (33, 34). However, a case of paternal UPD14 in a child with a normal karyotype and a mother with a rob(13;14)(q10;q10) has been recently described (35). The paternal UPD14 is postulated to be the result of fertilization of a nullisomy 14 egg by a normal haploid sperm, followed by monosomy rescue via post-zygotic duplication of the single paternal chromosome 14, resulting in duplicate ‘free’ chromosomes 14 with obligatory paternal iUPD (10). There is a second report of maternal UPD14 in a child with an i(14)(q10) and a father with a rob(13;14)(q10;q10) (36). In this case, the maternal UPD14 was postulated to be the result of fertilization of a normal haploid egg by a nullisomy 14 sperm, followed by monosomy rescue via post-zygotic duplication of the single maternal chromosome 14, resulting in isochromosome 14 formation with obligatory maternal iUPD (10). Although the mother was deceased and not available for analysis, chromosome 14 DNA polymorphic markers of the proband, father, and brother were interpreted as representing homozygosity for a maternal 14q. In addition, paternal cytogenetic analysis of maternal UPD15 PWS patients has been recently suggested to ensure that the father does not have a Robertsonian translocation, which could result in the contribution of a nullisomic 15 sperm (37). However, no specific cases were identified. Therefore, based on this new information, UPD studies are recommended in a foetus when a parent has a Robertsonian 14 and/or 15 translocation, regardless of whether the foetus has a normal or carrier karyotype (point 2).

In amniotic or CVS level III mosaicism, true mosaicism of the foetus is suggested. The clinical phenotype probably is the result of the trisomic/monosomic lines and confirmation of UPD might be clinically irrelevant (see points 3 and 4 above). Testing for UPD14 or 15 may be indicated, but the decision for chromosomes 6 and 7 is more difficult as UPD effects would probably be secondary to the clinical effects of the trisomy/monosomy line (3).

Prenatal testing should be considered in a foetus with:

1. a non-Robertsonian translocation between any chromosomes known to carry imprinted genes and at risk for 3:1 disjunction in which trisomy or monosomy rescue or gamete complementation could occur; and
2. anomalies detected on ultrasound consistent with a UPD phenotype, such as the ‘coat-hanger’ sign in UPD14. UPD may not be the only pathogenic mechanism resulting in such clinical signs and each centre will need to develop its own algorithm for testing to determine etiology.
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Risk of UPD

The risk of UPD in a foetus with a non-homologous, Robertsonian translocation that involves chromosomes 14 or 15 is approximately 0.6% (95% confidence interval (CI) 0.2–1.7%) (38).

The risk of UPD15 when trisomy 15 mosaicism has been detected, upon CVS or amniotic fluid analysis, has been estimated to range from 11% (1 case of UPD15 of 9 patients with confined placental mosaicism or CPM for chromosome 15) (39) to 29% (2 cases of UPD15 of 7 patients with CPM15) (40).

The risk of UPD in a foetus with 46,XX and 46,XY parents and a balanced, de novo homologousacrocentric rearrangement (i.e. either as a homologous Robertsonian translocation or an isochromosome) involving chromosomes 14 or 15, is approximately 66% (95% CI 22–96%) (10). The UPD in all cases, to date, is paternal, resulting from paternal isochromosome formation (10).

The risk of UPD15 in patients with a de novo, supernumerary inv dup(15) marker and variable clinical anomalies has been estimated at approximately 5% (3). This included 2 cases of UPD15 in 122 postnatal patients (1.6%) and 2 cases of UPD15 in 22 prenatal patients (7.7%) (41). However, it should be noted that: (i) almost all studies have been as a result of an abnormal phenotype; and (ii) the presence or absence of euchromatic material in the marker has not always been determined or reported (41). The presence of euchromatic material suggests that congenital anomalies and mental handicap will be present and that UPD is not clinically relevant (3). However, if there is no apparent euchromatic material, the presence of UPD becomes highly clinically relevant (3, 8).

To the best of our knowledge, no case of UPD recurrence has been reported to date. The recurrence risk after a child with UPD appears to be very low, such that invasive prenatal testing is not indicated (2).

Testing methodologies

The algorithm, establishment and validation of UPD testing and the definition of reporting standards are the responsibility of the molecular genetic laboratories performing the assays.

Conclusions

(1) UPD testing should be performed in conjunction with appropriate genetic counselling.
(2) Chromosomes of defined UPD clinical relevance include chromosomes 6 (paternal), 7 (maternal), 11 (paternal), 14 (maternal and paternal), and 15 (maternal and paternal).

Prenatal

(3) Prenatal UPD testing is recommended for a foetus presenting with any of the following cytogenetic abnormalities involving chromosomes with known imprinting effects: (i) level II or level III mosaicism for chromosomes 6, 7, 11, 14, or 15; (ii) familial and de novo balanced Robertsonian translocations and isochromosomes involving chromosomes 14 and 15; (iii) a normal karyotype when the parent has a Robertsonian 14 and/or 15 translocation; and (iv) de novo ESACs involving chromosomes 14 and 15 with no apparent euchromatic material.

(4) In prenatal cases with a non-Robertsonian translocation between any chromosomes known to carry imprinted genes and at risk for 3:1 disjunction in which trisomy/monosomy rescue or gamete complementation could occur, UPD testing should be considered.

Postnatal

(5) Postnatal UPD testing is recommended for patients presenting with a clinical phenotype that is compatible with any of the following cytogenetic abnormalities and known imprinting disorders: (i) familial and de novo Robertsonian translocations and isochromosomes involving chromosomes 14 and 15; (ii) de novo ESACs with no apparent euchromatic material involving chromosomes 14 and 15; and (iii) familial and de novo reciprocal non-Robertsonian translocations that involve chromosomes with known imprinting effects.

(6) UPD testing should be considered as part of the testing algorithm for patients presenting with features of disorders known to be associated with UPD, such as transient neonatal diabetes mellitus or clinical manifestations consistent with SRS.

(7) UPD testing should be considered for patients found to be homozygous for an autosomal or X-linked recessive disease causing mutation and only one parent is a carrier of the causative mutation, assuming that other potential explanations such as non-paternity, heterozygous deletion, testing artifact, etc. have been excluded.

(8) UPD testing should be considered for cases with apparent father–son transmission of an X-linked condition, assuming that other
potential explanations such as non-paternity, testing artifact, etc. have been excluded.

Future directions

The use of single nucleotide polymorphism (SNP) microarrays may become the method of choice in the identification of UPD for non-imprinted chromosomes. This would lead to the identification of recessive genes in the homozygous region(s) and may provide important diagnostic clues for both clinical phenotype and gene function.

References


