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Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG)

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OVERVIEW

In 1980, Eric Engel[1] first proposed the concept of uniparental disomy (UPD), in which both homologous chromosomes are inherited from one parent, with no contribution (for that chromosome) from the other parent. In 1988, the first case of a Mendelian disorder associated with UPD was reported, in which a child with cystic fibrosis (MIM 219700) had inherited two copies of a pathogenic variant in *CFTR* (MIM 602421) from a heterozygous carrier mother, with no contribution from the biological father.[2]

For the majority of chromosomes, UPD is without clinical consequence. However, for chromosomes 6, 7, 11, 14, 15, and 20, there are parent-of-origin or imprinting differences in gene expression in the context of UPD, which may lead to phenotypic abnormalities. In addition, UPD may uncover an autosomal recessive disorder on a chromosome that is not subject to imprinting, while UPD of the X chromosome may lead to X-linked recessive disorders in females. Rarely, inheritance of both sex chromosomes from the father, may result in father-to-son transmission of X-linked conditions.[3]

MECHANISMS AND CLINICAL CONSEQUENCES OF UPD

UPD generally results from two nondisjunction events, with the first event occurring during meiosis and the second being a mitotic event. Nondisjunction in meiosis I constitutes a failure of two homologues to segregate, which may eventually give rise to the presence of two different homologues from the same parent or heterodisomy. Nondisjunction in meiosis II is a failure of sister chromatids to separate into daughter cells, which subsequently can result in isodisomy. The gametes resulting from meiosis complicated by nondisjunction may be disomic (containing two copies of the affected chromosome) or nullisomic (containing no copies of the affected chromosome). Following fertilization with a normal haploid gamete, the zygote is expected to have either a trisomy or a monosomy for the affected chromosome. Postzygotic mitotic nondisjunction may then occur as the second event resulting in a rescue of the aneuploidy by either loss of the third chromosome (trisomy rescue) or duplication of a monosomic chromosome (monosomy rescue).[4] In addition, anaphase lag (the delayed movement

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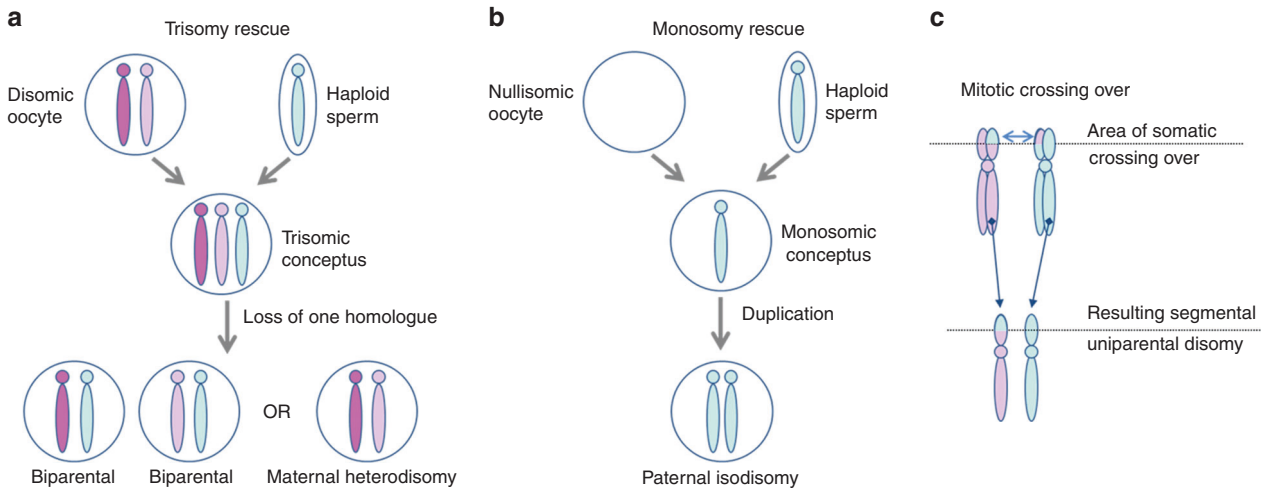

Fig. 1 Common mechanisms resulting in uniparental disomy (UPD). (**a**) Trisomy rescue mechanism. The example shows maternal nondisjunction in meiosis I resulting in a disomic oocyte. Upon fertilization with a normal sperm this produces a trisomic conceptus. Subsequent trisomy rescue theoretically results in UPD in one-third of the cases. (**b**) Monosomy rescue mechanism. The example shows maternal nondisjunction in meiosis I resulting in a nullisomic oocyte. Fertilization with a normal sperm produces a monosomic conceptus. Duplication of the only copy of the affected chromosome results in paternal isodisomy. (**c**) Mitotic crossing over. Somatic mitotic crossing over, resulting in mosaic segmental uniparental disomy. Pink shading, maternal chromosome; blue shading, paternal chromosome.

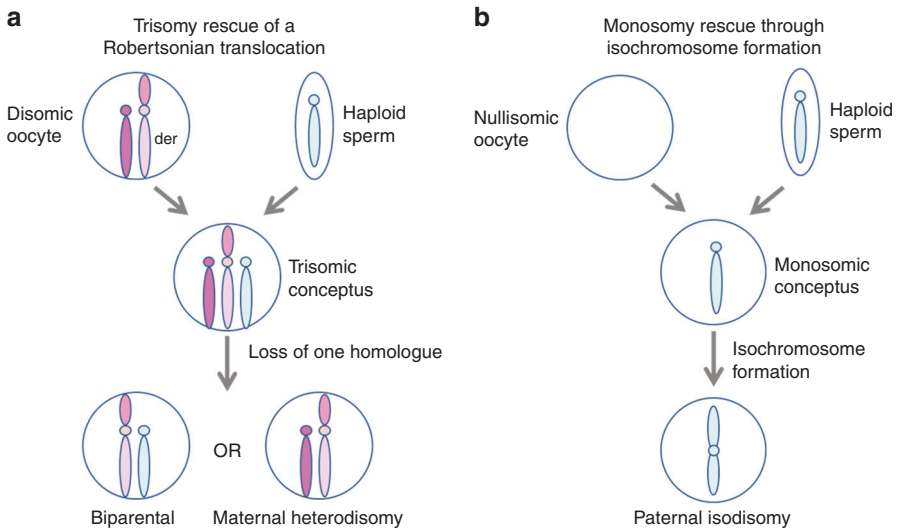

Fig. 2 Common mechanisms resulting in uniparental disomy (UPD) involving acrocentric chromosomal rearrangements. (**a**) Rescue of a trisomy conceptus from a Robertsonian translocation carrier mother. Disomy in the oocyte results from the presence of the derivative chromosome from the Robertsonian translocation (der) and a normal copy of one of the affected acrocentrics. Fertilization with a normal sperm produces a trisomic conceptus. The rescue results theoretically in UPD in 50% of the cases. (**b**) Monosomy rescue of a monosomic conceptus resulting from meiosis I nondisjunction and fertilization of a nullisomic gamete. Duplication (through isochromosome formation) of the only copy of a homologue would result in isodisomy in 100% of cases. Since the majority of nondisjunction occurs in maternal meiosis, most cases of isochromosomes arising through this mechanism result in paternal isodisomy. Pink shading, maternal chromosome; blue shading, paternal chromosome.

of a chromosome or chromatid during anaphase, leading to the loss of that chromosome in a daughter nucleus) may also be the second event leading to a trisomy rescue. Trisomy rescue with loss of the parental chromosome present in a single copy will result in the inheritance of both homologues of the affected chromosome from one parent or UPD (Fig. 1a). As the majority of nondisjunction occurs in maternal meiosis I,[5] it is more likely that a trisomy consists of two different maternal chromosomes and one paternal chromosome. Subsequent trisomy rescue through loss of a paternal chromosome will thus give rise to maternal heterodisomy. Meiotic recombination will often result in the presence of one or more regions of homozygosity (ROH) on the affected chromosome, but with retention of heterozygosity around the centromere where recombination is suppressed. Analogously, chromosomes inherited from the same parent in cases of isodisomy due to meiosis II errors often do not show complete homozygosity for all single-nucleotide polymorphism (SNP) markers. Due to meiotic recombination,

such chromosomes may also have alternating regions of heterozygosity and homozygosity, but in meiosis II errors, there is always homozygosity around the centromere. Postzygotic monosomy rescue (which is more rare than trisomy rescue) will result in complete isodisomy of the same homologue, with no heterodisomic regions (Fig. 1b). There are also cases of mosaic, segmental UPD affecting terminal regions of chromosome arms; they arise as postzygotic events, due to mitotic recombination between chromatids occuring in early embryogenesis (Fig. 1c). This UPD mechanism is responsible for a subset of cases of Beckwith–Wiedemann syndrome (BWS), an imprinting disorder resulting from altered activity of one or more genes in the imprinted gene cluster in the p15.5 region of chromosome 11 (as discussed later).[6]

Other rare mechanisms leading to UPD have been reported and include postfertilization error (via somatic recombination or gene conversion), gamete complementation, somatic replacement of a derivative chromosome, correction of interchange monosomy, and correction of a trisomy resulting in a small supernumerary marker chromosome (sSMC).[4] UPD has also been observed to result from the presence of structurally abnormal chromosomes, including Robertsonian translocations, isochromosomes, reciprocal translocations, derivative chromosomes, and inversions (Fig. 2).

As mentioned above, for the majority of chromosomes, there is no apparent phenotypic effect from UPD.[7] However, a few chromosomes contain regions with parent-specific gene expression (imprinting), and UPD of these chromosomes may lead to clinically recognizable consequences. Specific phenotypes have been well documented to date for maternal UPD for chromosomes 7, 11, 14, 15, and 20, and paternal UPD for chromosomes 6, 11, 14, 15, and 20. For some chromosomes (2 and 16 for example), it is still debated whether UPD has phenotypic effects attributable to imprinting. This uncertainty may be due to the subtle nature of the anomalies (e.g., maternal disomy 16),[8] conflicting reports in the literature (e.g., maternal disomy 2),[9] confounding mosaicism (e.g., maternal disomy 2 and 16), or too few cases reported.

The empiric risks for UPD following the observation of prenatal aneuploidy mosaicism for certain chromosomes or a prenatally diagnosed Robertsonian translocation have been reported. The chance that trisomy 15 mosaicism, observed prenatally as confined placental mosaicism on analysis of chorionic villus sampling (CVS), would result in UPD has been estimated to be 11% to 25%.[10–12] For prenatally identified Robertsonian translocations (de novo or inherited) between nonhomologous chromosomes (e.g., der[13;14]), the risk of UPD in the translocation carrier fetus is approximately 0.6%.[13,14] For homologous acrocentric rearrangements, for which the majority are de novo isochromosomes (i.e., chromosomes derived from a duplication of a single parental chromosome), the risk of UPD in the balanced carrier fetus is approximately 66%.[13]

The prevalence of UPD associated with a clinical presentation due to imprinting disorders or recessive diseases ranges from 1 in 3500 to 1 in 5000.[15,16] Recent data, collected using over four million consented research participants from the personal genetics company 23andMe and 431,094 northern European UK Biobank participants, estimated that UPD for all chromosomes (rather than just chromosomes carrying imprinted regions) occurs with an overall prevalence of 1 in 2000 births. Since the 23andMe database comprises, for the most part, healthy individuals from the general population, this is a more representative estimate of the overall UPD prevalence in the general population.[17]

TESTING METHODOLOGIES

Evaluation of DNA-based polymorphic markers is the typical approach to investigate UPD. Short tandem repeat (STR) markers are used for most UPD studies. These markers are abundant throughout the genome, many have very high heterozygosity values (a reflection of the allele frequency differences in the population), and they are ideally suited for multiplex polymerase chain reaction (PCR).[18–20] In addition to the proband's DNA sample, a sample from both parents is required to delineate the parental origin of the detected STR alleles. If both parents are not available, testing can be performed using one parent; however, in some cases, testing of a single parent may not completely rule out heterodisomy of the other parent. Multiple markers should be tested for each chromosome of interest.

It is strongly recommended that at least two fully informative loci, showing either UPD or biparental inheritance, should be identified for diagnostic reporting.[21] Multiple, highly polymorphic STR markers across each chromosome of interest should be selected based on their informativity and genomic location.[22–24] However, there are limitations to this technology in the detection of UPD in samples with somatic mosaicism, segmental UPD, and tissue-specific UPD. Diagnostic reporting should follow the International System for Human Cytogenomic Nomenclature (ISCN) 2016 guidelines: uniparental disomy is abbreviated as "upd" (lowercase), followed by the chromosome in parentheses, and then the parental origin.[25]

In clinical practice, UPD cases may be ascertained through testing for copy-number abnormalities using chromosomal microarray (CMA) platforms that have SNP probes. CMA can easily identify whole-chromosome isodisomy based on obligatory presence of extensive ROH on the affected chromosome including its pericentromeric region, but routine CMA analysis cannot determine the parental origin without testing parental samples. Furthermore, isodisomy constitutes only a small subset of UPD cases. Whole-chromosome heterodisomy is more common, and can be suspected in CMA testing based on its frequent association with ROH on the affected chromosome, generated by meiotic crossovers during meiosis in parental gametogenesis.[26] However, it has been shown that approximately one-third of all cases of molecularly confirmed UPD do not show extended ROH and are not detectable by CMA.[27] Even when present, ROH associated with heterodisomy varies in size, and overlap in the sizes has been demonstrated between ROH that was

associated with UPD, and ROH that occurred due to chance (identity by state) or parental consanguinity (identity by descent).[27] Laboratories should define size thresholds and other criteria for reporting ROH and recommending follow-up UPD testing. Terminal ROH has been shown to rarely occur in non-UPD cases, and may warrant reporting even when it is relatively small (5 Mb); for interstitial ROH, it has been proposed that larger size thresholds (15–20 Mb) may provide sufficient sensitivity without resulting in high false-positive rates.[27] Follow-up testing is indicated primarily if the ROH region is confined to one chromosome, involves one of the chromosomes that contain imprinted regions, and UPD for that chromosome is expected to result in an abnormal phenotype. Importantly, the ROH identified by CMA does not have to (and typically does not) overlap with the imprinted region on the affected chromosome. Regardless of where it localizes on the chromosome, the ROH in this situation functions as a marker of potential whole-chromosome UPD, which if confirmed will be responsible for the imprinting disorder in the patient. The presence of extended ROH on multiple chromosomes most commonly indicates a familial relationship between the proband's parents (consanguinity); recommendations for documenting suspected consanguinity as an incidental finding of genomic testing have been described elsewhere.[28]

Computational algorithms can also be employed to detect UPD through analysis of SNP distribution from trio genotype data in the context of exome or genome sequencing.[29,30] These tools have been used to identify whole-chromosome UPD and segmental UPD greater than 10 Mb from exome data.[31] Since heterozygous deletions can masquerade as segmental UPD, follow-up testing has to be performed to distinguish between these two abnormalities. In most clinical laboratories, evaluation for UPD is not routinely incorporated into clinical exome or genome sequencing assays. However, if UPD is detected during analysis, it can be reported as a secondary finding with a recommendation to confirm the finding with a clinically validated assay, for patients who consented to receive secondary findings.

Since these methodologies can potentially uncover misattributed relationships, this possibility should be addressed during the consent or pretest counseling process. Laboratories should develop a process for appropriate follow-up when misattributed relationships are suspected based on the UPD testing results.

In addition to techniques that directly detect UPD, multiple technologies are used in the diagnosis of imprinting disorders that can be caused by UPD for certain chromosomes but can also have other etiologies. Some of these techniques, like methylation-specific PCR (MS-PCR)[32] and methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA)[33] are based on interrogation of the methylation status of so-called differentially methylated regions (DMRs) or imprinting centers within the larger (typically several megabases in size) areas of chromosomes containing imprinted genes. DMRs have different methylation status on the maternal and the paternal homologue; they have been mapped, sequenced, and functionally characterized within well-known clinically significant imprinted chromosomal regions, and are thought to play a role in establishing and maintaining the parent-of-origin specific expression of the surrounding imprinted genes.[34] MS-PCR and MS-MLPA assays are designed to distinguish between the normal methylation profile of the DMRs on the chromosome of interest and the abnormal profile associated with an imprinting disorder, without the need for parental samples. However, neither technique can distinguish between UPD and imprinting defects. Thus, STR marker analysis is required to determine if UPD is the cause of the observed aberrant methylation pattern.

CHROMOSOMES OF CLINICAL RELEVANCE

UPD for any chromosome is associated with an increased risk for a recessive disorder, since it can result in an affected child when only one parent is a carrier of a pathogenic variant. This is true even for cases of heterodisomy, due to isodisomic regions generated through meiotic crossovers during gametogenesis in the parent. Individuals at risk for a recessive disorder due to a UPD event may be ascertained by CMA testing. Further evaluation for a recessive disorder may be recommended if there is a concern for UPD based on large ROH on a single chromosome detected by CMA testing, in particular if there is also a clinical suspicion for a recessive condition based on a physical examination or results of other auxiliary diagnostic studies. More often the occurrence of a recessive disorder due to UPD is identified when sequencing based testing shows homozygosity for a pathogenic variant for which only one parent is a carrier.

UPD for specific chromosomes results in abnormal phenotypes shown to be caused by imprinting.

Paternal UPD6 and transient neonatal diabetes mellitus

Transient neonatal diabetes mellitus (TNDM, MIM 601410) is a rare but well recognized type of diabetes caused by overexpression of the imprinted loci *PLAGL1* and *HYMAI* at chromosome 6q24.2.[35,36] Partial or complete paternal UPD6 including *PLAGL1* and *HYMAI* has been reported in approximately 40% of cases of TNDM.[37] The finding of macroglossia or other congenital anomalies in addition to TNDM is a strong indicator to suspect UPD.[37] The majority of paternal UPD6 is isodisomic and therefore affected individuals are at increased risk for rare autosomal recessive disorders including *HFE*-associated hereditary hemochromatosis (MIM 235200), methylmalonic acidemia (MIM 251000), and congenital adrenal hyperplasia caused by 21-hydroxylase deficiency (MIM 201910).[37]

Maternal UPD7 and Russell–Silver syndrome

Russell–Silver syndrome (RSS, MIM 180860) is characterized by prenatal and postnatal poor growth, relative macrocephaly,

and limb, body, and/or facial asymmetry. Complete and partial maternal UPD7 accounts for ~7–10% of patients with RSS.[38–42] Partial UPD7 due to segmental maternal UPD restricted to the long arm of chromosome 7, which results in hypermethylation of the imprinting center of the *MEST* gene within 7q32.2, was reported in several RSS patients.[43] Maternal UPD7 isodisomy and maternal heterodisomy have been reported in RSS patients.[41,44] Mosaic maternal segmental UPD of 7q has also been reported in some cases.[45,46]

Paternal UPD11 and Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome (BWS, MIM 130650) is a congenital overgrowth disorder with a predisposition to tumorigenesis. The disorder is caused by abnormalities within the two differentially methylated regions (DMRs) on the short arm of chromosome 11: imprinting center 1 (IC1), which regulates the expression of *H19* and *IGF2*, and imprinting center 2 (IC2), which regulates the expression of *CDKN1C*, *KCNQ1*, and *KCNQ10T1*. The common causes of BWS are methylation abnormalities affecting the imprinting centers.[47] Segmental paternal UPD of 11p15 occurs in about 20% of BWS patients and results in biallelic expression of the normally paternally expressed *IGF2* (in IC1 region), encoding a potent fetal growth factor.[48] The UPD appears to consistently arise from a somatic recombination event resulting in paternal isodisomy (Fig. **1c**). It has been hypothesized that nonmosaic whole-chromosome UPD11 may be lethal, and in fact, mosaicism is present in the majority of the cases, confirming the postzygotic origin of this UPD.[6] The detection of nonmosaic ROH involving chromosome 11 in a prenatal setting may be concerning about the high likelihood of fetus lethality.

Maternal UPD11 and Russell–Silver syndrome

Maternal UPD of chromosome 11 has been rarely described as the cause of isolated cases of RSS.[49–52] Chromosome 11p15-related RSS is associated primarily with hypomethylation of IC1; this leads to biallelic expression of H19 and biallelic silencing of *IGF2*, resulting in growth restriction.[52] Fewer than ten cases of RSS due to maternal UPD11 have been reported to date.[49–51] The phenotype is indistinguishable from RSS cases caused by other mechanisms, and includes growth restriction, asymmetry, and relative macrocephaly; all reported cases showed mosaicism, consistent with the postzygotic origin of this UPD.[50,51] It has been hypothesized that mosaic maternal UPD11 may be a more common cause of RSS than is currently appreciated.[51] However, this abnormality is very difficult to detect, either due to low levels of mosaicism or because it frequently involves tissues other than the peripheral blood cells most often sampled for testing.[50,51]

Maternal UPD14 and Temple syndrome

Temple syndrome (TS, MIM 616222) is characterized by pre- and postnatal poor growth, mild developmental delay, hypotonia, hyperextensible joints, small hands and feet, truncal obesity, precocious or early onset of puberty, and adult short stature.[53] Maternal UPD14 is the most widely recognized cause of TS; it results in loss of expression of all paternally expressed genes (*DLK1*, *RTL1*, and *DIO3*) and overexpression of maternally expressed genes (noncoding RNAs *GTL2/MEG3, MEG8, RTL1as*, and additional microRNAs [miRNAs] and small nucleolar RNAs [snoRNAs]) at chromosome 14q32.2.[54,55] In rare cases, maternal UPD14 has been reported in association with mosaicism,[56] Robertsonian translocations,[57] and sSMC.[58]

Paternal UPD14 and Kagami–Ogata syndrome

Kagami–Ogata syndrome (KOS, MIM 608149) is characterized by a severe phenotype with polyhydramnios, large omphalocele, thoracic dysplasia (coat-hanger sign on X-rays) with respiratory failure, abdominal wall defects, poor growth, developmental delay, and facial abnormalities including full cheeks and protruding philtrum.[59] Paternal UPD14 accounts for approximately two-thirds of KOS patients; the remaining cases have been associated with microdeletions affecting the maternal chromosome 14 and epigenetic defects.[59,60] Excessive *RTL1* expression and absent *MEG* expression in the q32.2 region of chromosome 14 constitute the primary underlying factors for the phenotypic abnormalities in these patients.[59,60]

Maternal UPD15 and Prader–Willi syndrome

Prader–Willi syndrome (PWS, MIM 176270) is characterized by neonatal hypotonia and poor suck with failure to thrive, developmental delay and/or intellectual disability, childhood-onset obesity, short stature, hypogonadism, and behavior problems. Maternal UPD15 is the second most common finding in patients with PWS and accounts for approximately 20–30% of the cases.[61] Patients with maternal UPD15 lack the activity of imprinted, paternally expressed genes in the 15q11.2-q13 region (*MKRN3*, *MAGEL2*, *NDN*, *SNURF-SNRPN*, and several snoRNA genes) and have overexpression of maternally expressed genes (*UBE3A* and *ATP10C*).[62–64] Maternal nondisjunction events resulting in UPD15-PWS are associated with meiosis I errors, with rare cases originating from meiosis II or due to postzygotic errors.[65] Maternal UPD15 has been found in association with Robertsonian translocations, mosaicism, isochromosomes, and sSMC involving chromosome 15.

Paternal UPD15 and Angelman syndrome

Angelman syndrome (AS, MIM 105830) is associated with severe intellectual disability with absent speech, ataxic movements and gait, increased tone after infancy, microcephaly, seizures, and a happy disposition with paroxysmal laughter. Paternal UPD15 accounts for approximately 3–7% of AS cases. Patients with paternal UPD15 lack the activity of the maternally expressed *UBE3A* and *ATP10C* genes, within the 15q11.2-q13 region. Imprinted *UBE3A* expression is restricted to brain cells,

and the lack of its expression from the maternal chromosome 15 is considered to be the major cause of the disease phenotype.[66] Generally, paternal UPD15 cases associated with AS reflect isodisomic UPD as a consequence of a postzygotic mitotic error, though cases due to errors at meiosis II (MII) also occur.[65] Paternal UPD15 may be rarely due to a parental Robertsonian translocation or isochromosomes.[67,68]

Maternal UPD20 and Mulchandani–Bhoj–Conlin syndrome

Maternal UPD of chromosome 20 (Mulchandani–Bhoj–Conlin syndrome, MIM 617352), without evidence of trisomy 20 mosaicism, is a rare disorder with fewer than 20 patients reported in the literature. The condition is characterized by intrauterine and postnatal poor growth and prominent feeding difficulties with failure to thrive. Most patients do not have dysmorphic features, congenital abnormalities, or major developmental delay. There is a significant phenotypic overlap with RSS and other conditions that predominantly exhibit pre- and postnatal poor growth and short stature. Unexpectedly, in the majority of published cases, CMA testing had genotyping patterns suggesting UPD due to meiosis II error or postzygotic mitotic error, rather than the typically more common meiosis I nondisjunction.[69,70]

Paternal UPD20

Paternal UPD of chromosome 20 results in pseudohypoparathyroidism type 1b (PHP1B, MIM 603233), which is characterized by resistance to parathyroid hormone in kidneys and presents as hypocalcemia, hyperphosphatemia, and abnormally high parathyroid hormone levels. The condition typically results from deletions in the DMR of the *GNAS* locus on 20q, or a deletion in the *STX* gene, which acts as a long-range control element of methylation at the *GNAS* locus. These defects result in the absence of expression of the maternal Gs-α isoform in renal tissues. Rare cases where PHP1B was caused by paternal UPD20 have been reported.[71]

INDICATIONS FOR POSTNATAL UPD TESTING

Clinicians may order postnatal UPD testing to confirm a clinical suspicion of a diagnosis based on a constellation of clinical and physical findings. Confirmation of a diagnosis is important to discuss recurrence risk with the family as well as the clinical course and the prognosis of the condition.

Recommendations for postnatal UPD testing include:

1. Patients evaluated for developmental delay/intellectual disability with or without congenital anomalies and found to have a familial or de novo balanced Robertsonian translocation involving chromosome 14 or 15.[72]
2. Patients evaluated for developmental delay/intellectual disability with or without congenital anomalies and found to have a supernumerary structurally abnormal chromosome derived from chromosome 14 or 15.[73]
3. Patients with homozygosity for a pathogenic variant causing an autosomal recessive disorder when only one parent is a carrier for that variant, in the absence of other explanations such as intragenic deletion and misattributed relationships.[74]
4. Patients with TNDM and hypomethylation within the 6q24 DMR region. Testing for UPD6 can be ordered sequentially or simultaneously with MS-MLPA.[37,75]
5. Patients with clinical suspicion for RSS. Testing for UPD7 can be ordered sequentially or simultaneously with methylation testing of the IC1 on chromosome 11p15.[52,76,77]
6. Patients with BWS found to have loss of methylation at IC2 and gain of methylation at IC1 at 11p15. It should be noted that first-line molecular testing for BWS should include DNA methylation analysis of IC1 and IC2.[23]
7. Patients with clinical findings and physical features suggestive of maternal or paternal UPD14. The UPD testing can be ordered sequentially to or simultaneously with the methylation testing.[72,73]
8. Patients with PWS or AS with abnormal methylation studies (other than MS-MLPA) who have normal karyotype and CMA results.[78] Although large ROH observed by CMA testing is highly suspicious for UPD, it requires confirmation using other methods. It is important to keep in mind that DNA methylation analysis is the first-line testing for PWS and AS.[78]
9. Patients with PHP1B who have abnormal methylation studies of the DMRs at the GNAS complex locus with normal karyotype and CMA results. In addition, patients with poor growth and feeding difficulties found to have ROH for chromosome 20 on SNP array.
10. Female patients who present with unexplained severe manifestations of X-linked conditions and who are found to have homozygosity for a pathogenic variant in an X-linked gene.[74]
11. Male patients with unexplained father-to-son transmission of an X-linked disorder.[3]

INDICATIONS FOR PRENATAL UPD TESTING

Clinicians may order prenatal UPD testing when other prenatal studies, performed for advanced maternal age or because of a known familial chromosomal aberration, raise concerns for UPD. UPD analysis may also be used to confirm a clinical suspicion of a diagnosis based on a constellation of prenatal ultrasonographic findings. Confirmation of a diagnosis is important in order to discuss the clinical course and the prognosis of the condition and can be used later for genetic counseling purposes when the recurrence risk is discussed with the family. Timing and turnaround time are critical compared with postnatal testing because of the limited time available for decision making.

Recommendations for prenatal UPD testing include:

1. Level II or level III mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 in amniocentesis or CVS.[79]

2. Level II or level III mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 in CVS followed by normal karyotype in amniocentesis.[80]

   (Note: Level II (multiple cell pseudomosaicism)[81]: same abnormality observed in two or more cells (flask method) or in two or more cells from one or more colonies (in situ) in the same culture.[82] Level III (true mosaicism)[81]: two or more cells with the same abnormality observed in two or more independent cultures.)

3. In the context of preimplantation genetic screening (PGS), a transfer of mosaic embryos with trisomy or monosomy of chromosomes 6, 7, 11, 14, 15, or 20 should be followed by prenatal studies including UPD testing.[83–85] Since embryos with a completely normal karyotype are rare in the context of PGS, detection of mosaic aneuploidy does not prohibit transfer. As discussed under UPD mechanisms, one of the processes that leads to mosaicism may involve an initially abnormal conceptus, typically due to a meiotic error, with a subsequent rescue mechanism via a mitotic event generating a normal cell line. Timing of the rescue will determine the distribution of the normal and the abnormal cell lines in the fetus and the placenta. For embryos with mosaicism, rescue may generate a fetus with a normal karyotype but with a risk for UPD.
4. Prenatal imaging anomalies consistent with a UPD phenotype. The classic example is the pathognomonic coat-hanger sign in paternal UPD14.[86] Omphalocele, macroglossia, visceromegaly, enlarged adrenals, or macrosomia with no obvious mechanism are also typical prenatal findings in BWS.[87] Native amniotic fluid is the preferred tissue for UPD11 testing but the degree of mosaicism may not correlate with the true mosaicism in the fetus and therefore the prediction of postnatal phenotypic outcome is challenging. Furthermore, in the case of negative results the presence of mosaic UPD cannot be excluded.[80] On the other hand, fetal growth restriction can be considered as a relative indication to test for RSS or Mulchandani–Bhoj–Conlin syndrome but this finding is relatively common and its presence alone should not be an indication.
5. Familial or de novo balanced Robertsonian translocation or isochromosome involving chromosome 14 or 15 based on CVS or amniocentesis.[72,88,89] Both familial and de novo translocations are associated with an increased risk for UPD.
6. De novo sSMC with no apparent euchromatic material in the fetus.[90,91]
7. Non-Robertsonian translocation between an imprinted chromosome with possible 3:1 disjunction that can lead to trisomy or monosomy rescue or gamete complementation. Although every chromosome abnormality that increases the occurrence of nondisjunction in theory would increase the risk for UPD of the chromosomes involved, there are only very few cases reported.[38,92]

SUMMARY OF CLINICAL AND DIAGNOSTIC CONSIDERATIONS

1. Chromosomes of known clinical relevance for UPD include 6, 7, 11, 14, 15, and 20.
2. UPD testing should be considered for:

   a. Evaluation of a subject with clinical, physical, or ultrasonographic features of disorders known to be associated with UPD.
   b. Molecular investigation of a condition that does not follow a typical Mendelian inheritance pattern including recessive and X-linked disorders.
   c. Prenatal or postnatal identification of a structurally abnormal chromosome 14 or 15.
   d. Prenatal trisomy or monosomy mosaicism of a chromosome known to be associated with a UPD phenotype.

3. Testing should be performed on DNA collected from the child/fetus and at least one parent using polymorphic markers.
4. UPD can be ascertained through analysis of SNP distribution from trio genotype data in the context of exome or genome sequencing. However, unless the UPD analysis is validated by the diagnostic laboratory for clinical use, confirmation by a clinically validated STR-based assay is required. Detection of isodisomic UPD by CMA warrants clinical correlation and further testing to determine parent of origin.
5. Reporting of results includes at least two fully informative markers from each chromosome of interest and uses the current ISCN guidelines.[25]

DISCLOSURE

D.d.G., C.A., M.K.T., K.L.D., and G.R. all serve as directors in clinical laboratories that perform a breadth of genetic and genomic analyses on a fee-for-service basis. M.S. declares no conflicts of interest.

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