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## **CCMG Guidelines: Prenatal and Postnatal Diagnostic Testing for Uniparental Disomy (UPD)**

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**PURPOSE:** The aim of this statement is to provide clinicians, cytogeneticists and molecular geneticists of the Canadian College of Medical Geneticists (CCMG) a comprehensive review of the role of UPD in constitutional genetic diagnosis and to provide a guideline as to when investigation for UPD is recommended.

**METHODS OF STATEMENT DEVELOPMENT:** Members of the CCMG Cytogenetics, Molecular Genetics, Clinical Practice, and Prenatal Diagnosis committees reviewed the relevant literature on uniparental disomy (UPD) in constitutional genetic diagnosis. Guidelines were developed for UPD testing in Canada. The guidelines were circulated for comment to the CCMG members-at-large and, following appropriate modification, approved by the CCMG Board of Directors on July 13, 2010.

## **INTRODUCTION**

Uniparental disomy (UPD) is defined as the inheritance or presence of both homologous chromosomes of a pair from one parent and no copy from the second parent in a diploid genome (Engel, 1980). 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 (Kotzot, 2008b).

UPD is rare, as it generally requires two independent chromosome nondisjunction 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 (Kotzot, 2008a,b).

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 (Engel, 2006); post-fertilization error (by somatic recombination or gene conversion), resulting in segmental UPD (Engel, 2006; Kotzot, 2008b); somatic replacement of a derivative chromosome (Shaffer et al, 2001); 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 (Robinson et al, 1993; James et al, 1995; Engel, 2006; Kotzot, 2008b). For example, chromosome 15 ESACs comprised entirely of heterochromatin have been associated with UPD 15 and likely represent the remnants of a trisomy rescue (Liehr et al, 2005).

The majority of nondisjunction occurs in maternal meiosis I (Koehler et al, 1996). 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 non-disjunction and any regions of isodisomy likely 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 postzygotic duplication of the single paternal chromosome, either as a duplicate 'free' chromosome or usually resulting in isochromosome formation, with obligatory paternal iUPD (Berend et al, 2000).

UPD for the majority of chromosomes is without phenotypic effect (Kotzot, 1999). The clinical consequences associated with UPD are three fold. First, UPD for a few chromosome segments can result in clinically recognizable developmental abnormalities due to imprinting effects through parent-of-origin differences in gene expression. Second, the presence of homozygosity in iUPD, representing duplicate copies of a single parental chromosome, may result in two copies of a recessive mutation from the heterozygous carrier parent with the consequent recessive genetic disorder in the child. Third, UPD resulting from trisomy rescue is often associated with placental or fetal 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 (Kotzot, 2008a) and, because these genes are almost always clustered, there are fewer imprinted chromosome regions (Kotzot, 2008a). Thus far, only five chromosomes have been defined as imprinted based on the associated clinical phenotypes and synteny with mouse chromosomes (Kotzot, 2008a): chromosomes 6, 7, 11, 14, and 15.

Paternal UPD 6 has been reported in approximately 20% of cases with transient neonatal diabetes mellitus (DMTN) (Shaffer et al, 2001), which is generally associated with intrauterine growth retardation (IUGR) and macroglossia (Kotzot, 2008a). 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 (Shield and Temple, 2002).

Maternal UPD 7 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 (Shaffer et al, 2001; Kotzot, 2008a). The outcome of children with maternal UPD 7 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 (Kotzot et al, 2000). Reports of maternal UPD 7 and poor outcome are associated with additional complications, such as trisomy 7 mosaicism (Kotzot et al, 2000).

Segmental paternal iUPD of 11p15 has been identified in approximately 20% of patients with Beckwith-Wiedemann syndrome (BWS), an overgrowth syndrome characterized by macroglossia, organomegaly, omphalocele, and an increased risk for embryonal tumours (Shaffer et al, 2001; Kotzot, 2008a). The segmental iUPD of 11p15 indicates that the UPD in BWS is due to a post-fertilization error (by somatic recombination or gene conversion). Mosaic full paternal UPD11 has been associated with severe IUGR (Webb et al, 1995) and a single case of mosaic full paternal UPD11 has been seen with typical BWS (Dutly et al, 1998). Mosaic segmental maternal UPD11 for 11q13->qter has been reported in a single case complicated by mosaic trisomy of the same chromosome segment (Kotzot et al, 2001). In addition, chromosome 11p15 abnormalities involving methylation defects and maternal duplications have been reported in approximately 64% of SRS patients (Gicquel et al, 2005; Abu-Amero et al, 2008). Mosaic, full maternal UPD11 has also been reported in a patient with SRS (Bullman et al, 2008).

Maternal UPD 14 results in individuals with short stature, hypotonia, precocious puberty, post pubertal truncal obesity, and small hands and feet. Paternal UPD 14 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. UPD 14 has been reported in association with Robertsonian translocations, mosaicism, isochromosomes, and ESACs involving chromosome 14 (Shaffer et al, 2001; Mitter et al, 2006; Kotzot, 2008a).

Maternal and paternal UPD 15 represent the most frequently observed UPD (Kotzot, 2008a). Prader-Willi syndrome (PWS) is characterized by facial dysmorphism, neonatal hypotonia and poor suck with failure to thrive, followed by hyperphagia with subsequent obesity, developmental delay, moderate mental retardation, and short stature. Approximately 70-75% of PWS results from a paternal deletion of 15q11.2-q13. Maternal UPD 15 also results in PWS and accounts for approximately 25-30% of cases. Imprinting center defects have been reported in <1-3% of PWS patients (Shaffer et al, 2001; Gene Tests, 2008a; Kotzot, 2008a). Angelman syndrome (AS) is characterized by severe mental retardation, ataxia, seizures, and a happy disposition with inappropriate laughter. A maternal deletion of 15q11.2-13 is present in approximately 68-70% of AS patients. Paternal UPD 15 also results in AS, but accounts for only 3-7% of cases. Approximately 3-5% of AS cases have an imprinting center defect, and approximately 5-11% have mutations in the ubiquitin-protein 3A ligase (UBE3A) gene. The remaining 10-15% of AS patients have no identifiable genetic defect (Shaffer et al, 2001; Gene Tests, 2008b; Kotzot, 2008a). UPD 15 has been reported in association with Robertsonian translocations, mosaicism, isochromosomes, and ESACs involving chromosome 15 (Robinson et al, 1993; James et al, 1995; Shaffer et al, 2001; Kotzot, 2008a).

## **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 fetus (Chudoba et al, 1999; Shaffer et al, 2001; Wolstenholme et al, 2001; Robinson et al, 2005; Langlois et al, 2006; Kotzot, 2008a).

## **INDICATIONS FOR POSTNATAL UPD TESTING**

Postnatal UPD testing is done 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 in:

- 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;
- newborns with neonatal diabetes mellitus;
- patients with clinical features suggestive of maternal or paternal UPD14; and
- 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.

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 (Smeets et al, 1992; Smith et al, 1994; Calounova et al, 2006). Because the association between uniparental disomy and reciprocal translocation may exist with an under-estimated frequency, UPD testing should still be considered (Dupont et al, 2002).

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:

- SRS and a normal karyotype;
- BWS and a normal karyotype; and
- 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 done to provide a diagnosis in clinical situations at increased risk for an imprinting disorder. Testing should be done in a timely manner due to the limited time available for decision making.

Prenatal testing is recommended in fetuses with:

- 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 (Antonarakis et al, 1993);
- a normal karyotype when the parent is a carrier of a balanced Robertsonian translocation of chromosomes 14 and/or 15\*;
- level II or level III\*\* amniotic fluid mosaicism for trisomy or monosomy of chromosomes 6, 7, 11, 14, or 15; and
- level II or level III\*\* 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 fetus with a parent who is the carrier of a balanced Robertsonian translocation does not indicate a significant risk for UPD, although studies to date are of too small sample size to achieve statistical significance (Silverstein et al, 2002; Ruggeri et al, 2004). 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 (Potok et al, 2009). 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 postzygotic duplication of the single paternal chromosome 14, resulting in duplicate 'free' chromosomes 14 with obligatory paternal iUPD (Berend et al, 2000). 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) (Tomkins et al, 1996). 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 postzygotic duplication of the single maternal chromosome 14, resulting in isochromosome 14 formation with obligatory maternal iUPD (Berend et al, 2000). 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 (Cassidy and Driscoll, 2009). However, no specific cases were identified. Therefore, based on this new information, UPD studies are recommended in a fetus when a parent has a Robertsonian 14 and/or 15 translocation, regardless of whether the fetus has a normal or carrier karyotype.

\*\*In amniotic or CVS level III mosaicism, true mosaicism of the fetus is suggested. The clinical phenotype likely is the result of the trisomic/monosomic lines and confirmation of UPD might be clinically irrelevant. Testing for UPD 14 or 15 may be indicated, but the

decision for chromosomes 6 and 7 is more difficult as UPD effects would likely be secondary to the clinical effects of the trisomy/monosomy line (Kotzot, 2008a).

Prenatal testing should be considered in a fetus with:

- 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
- anomalies detected on ultrasound consistent with a UPD phenotype, such as the “coat-hanger” sign in UPD 14. 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.

### **RISK OF UPD**

The risk of UPD in a fetus with a non-homologous, Robertsonian translocation that involves chromosomes 14 or 15 is approximately 0.6% (95% CI 0.2-1.7%) (Shaffer, 2006).

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) (EUCHROMIC, 1999 ) to 29% (2 cases of UPD15 of 7 patients with CPM15) (Christian et al, 1996).

The risk of UPD in a fetus with 46,XX and 46,XY parents and a balanced, *de novo* homologous acrocentric rearrangement (i.e. either as a homologous Robertsonian translocation or an isochromosome) involving chromosomes 14 or 15, is approximately 66% (95% CI 22%-96%) (Berend et al, 2000). The UPD in all cases, to date, is paternal, resulting from paternal isochromosome formation (Berend et al, 2000).

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% (Kotzot, 2008a). This included 2 cases of UPD15 in 122 postnatal patients (1.6%) and 2 cases of UPD15 in 22 prenatal patients (7.7%) (Kotzot et al, 2002a). However, it should be noted that: a) almost all studies have been as a result of an abnormal phenotype; and b) the presence or absence of euchromatic material in the marker has not always been determined or reported (Kotzot, 2002a). The presence of euchromatic material suggests that congenital anomalies and mental handicap will be present and that UPD is not clinically relevant (Kotzot, 2008a). However, if there is no apparent euchromatic material, the presence of UPD becomes highly clinically relevant (Liehr et al, 2005; Kotzot, 2008a).

## **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. Chromosomes of defined UPD clinical relevance include chromosomes 6 (paternal), 7 (maternal), 11 (paternal), 14 (maternal and paternal), and 15 (maternal and paternal).

## **PRENATAL**

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

4. 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: a) familial and *de novo* Robertsonian translocations and isochromosomes involving chromosomes 14 and 15; b) *de novo* ESACs with no apparent euchromatic material involving chromosomes 14 and 15; and c) familial and *de novo* reciprocal non-Robertsonian translocations that involve chromosomes with known imprinting effects.
5. 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 Silver-Russell syndrome.

6. UPD testing should be considered for patients found to be homozygous for an autosomal 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.

## **REFERENCES**

- Abu-Amero S, Monk D, Frost J, Preece M, Stanier P, Moore GE. 2008. The genetic etiology of Silver-Russell syndrome. *J Med Genet* 45:193-199.
- Antonarakis SE, Blouin JL, Maher J, Avramopoulos D, Thomas G, Talbot CC Jr. 1993. Maternal uniparental disomy for human chromosome 14, due to loss of a chromosome 14 from somatic cells with t(13;14) trisomy 14. *Am J Hum Genet* 52:1145-1152.
- Berend SA, Horwitz J, McCaskill C, Shaffer LG. 2000. Identification of uniparental disomy following prenatal detection of Robertsonian translocations and isochromosomes. *Am J Hum Genet* 52:8-16.
- Bullman H, Lever M, Robinson DO, Mackay DJG, Holder SE, Wakeling EL. 2008. Mosaic maternal uniparental disomy of chromosome 11 in a patient with Silver-Russell syndrome. *J Med Genet* 45:396-399.
- Calounova G, Novotna D, Simandlova M, Havlovicova M, Zumrova A, Kocarek, Sediacek Z. 2006. Prader-Willi syndrome due to uniparental disomy in a patient with a balanced chromosomal translocation. *Neuro Endocrinol Lett* 27:579-585.
- Cassidy SB and Driscoll DJ. 2009. Prader-Willi syndrome. *Eur J Hum Genet* 17:3-13.
- Christian SL, Smith AC, Macha M, Black SH, Elder FF, Johnson JM, Resta RG, Surti U, Suslak L, Verp MS, Ledbetter DH. 1996. Prenatal diagnosis of uniparental disomy 15 following trisomy 15 mosaicism. *Prenat Diagn.* 16:323-32.
- Chudoba I, Franke Y, Senger G, Sauerbrei G, Demuth S, Beensen V, Neumann A, Hansmann I, Claussen I. 1999. Maternal UPD 20 in a hyperactive child with severe growth retardation. *Eur J Hum Genet* 7:533-540
- Dupont JM, Cuisset L, Cartigny M, Le Tessier D, Vasseur C, Rabineau D, Jeanpierre M. 2002. Familial Reciprocal Translocation t(7;16) associated with Maternal Uniparental Disomy 7 in a Silver-Russell Patient. *Am J Med Genet* 111:405-408.
- Dutly F, Baumer A, Kayserili H, Yuksel-Apak M, Zerova T, Hebisch G, Schintzel A. 1998. Seven cases of Wiedemann-Beckwith syndrome, including the first reported case of mosaic paternal isodisomy along the whole chromosome 11. *Am J Med Genet* 79: 347-353.

Engel E. 1980. A new genetic concept: uniparental disomy and its potential effect: isodisomy. *Am J Med Genet* 6:137-142.

Engel E. 2006. A fascination with chromosome rescue in uniparental disomy: Mendelian recessive outlaws and imprinting copyrights infringements. *Eur J Hum Genet* 14:1158-1169.

EUCROMIC: European Collaborative Research on Mosaicism in CVS. 1999. Trisomy 15 CPM: probable origins, pregnancy outcome and risk for fetal UPD. *Prenat Diag* 19:29-35.

Gene Tests. 2008a.

<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pws>

Gene Tests. 2008b.

<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=angelman>

Gicquel C, Rossignol S, Cabrol S, Houang M, Steunou V, Barbu V, Danton F, Thibaud N, Le Merrer M, Burglen L, Bertrand AM, Netchine I, Le Bouc Y. 2005. Epimutation of the telomeric imprinting center region on chromosome 11p15 in Silver-Russell syndrome. *Nat Genet* 37:1003–7.

ISCN (An International System for human Cytogenetics Nomenclature). 2009. Shaffer LG, Tommerup N (eds). S Karger, Basel.

James RS, Temple IK, Dennis NR, Crolla JA. 1995. A search for uniparental disomy in carriers of supernumerary marker chromosomes. *Eur J Hum Genet* 3:21-26.

Kalousek DK, Langlois S, Barrett I, Yam I, Wilson DR, Howard-Peebles PN, Johnson MP, Giorgiutti E. 1993. Uniparental Disomy for Chromosome 16 in Humans. *Am J Hum Genet* 52:8-16

Koehler KE, Hawley RS, Sherman S, Hassold T. 1996. Recombination and nondisjunction in humans and flies. *Hum Mol Genet* 5:1495-1504.

Kotzot D. 1999. Abnormal phenotypes in uniparental disomy (UPD): fundamental aspects and a critical review with bibliography of UPD other than 15. *Am J Med Genet* 82:265-274.

Kotzot D, Balmer D, Baumer A, Chrzanowska K, HAamel BC, Ilyina H, Krajewska-Walasek M, Luire IW, Otten BJ, Schoenle E, Tariverdian G, Schinzel A. 2000. Maternal uniparental disomy 7 – review and further delineation of the phenotype. *Eur J Pediatr* 159:247-256.

- Kotzot D, Rothlisberger B, Riegel M, Schinzel A. 2001. Maternal uniparental disomy 11q13->qter in a dysmorphic and mentally retarded female with partial trisomy mosaicism 11q13->qter. *J Med Genet* 38:876-881.
- Kotzot D. 2002a. Supernumerary marker chromosomes (SMC) and uniparental disomy (UPD): co-incidence or consequence? *J Med Genet* 39:775-778.
- Kotzot 2002b. Review and meta-analysis of systemic searches for uniparental disomy (UPD) other than UPD15. *Am J Med Genet* 11:366-375.
- Kotzot D. 2008a. Prenatal testing for uniparental disomy: indications and clinical relevance. *Ultrasound Obstet Gynecol* 31:100-105.
- Kotzot D. 2008b. Complex and segmental uniparental disomy updated. *J Med Genet* 45:545-556.
- Langlois S, Yong PJ, Yong SL, Barrett I, Kalousek DK, Miny P, Exeler R, Morris K, Robinson WP. 2006. Postnatal follow-up of prenatally diagnosed trisomy 16 mosaicism. *Prenat Diagn* 26:548-558.
- Liehr T, Brude E, Gillissen-Kaesbach G, Konig R, Mrasek K, von Eggeling F, Starke H. 2005. Prader-Willi syndrome with a karyotype 47,XY,+min(15)(pter->q11.1) and maternal UPD15 – case report plus review of similar cases. *Eur J Med Genet* 48:175-181.
- Mitter D, Buiting K, von Eggeling F, Kuechler A, Liehr T, Mau-Holzmann UA, Prott EC, Wieczorek D, Gillissen-Kaesbach G. 2006. Is there a higher incidence of maternal uniparental disomy 14 [upd(14)mat]? Detection of 10 new patients by methylation-specific PCR. *Am J Med Genet* 140A:2039-2049.
- Potok OV, Schlade-Bartusiak K, Perrier R, Chrnos JE, Shetty S, Parboosingh J, Lauzon J. 2009. Paternal uniparental isodisomy for chromosome 14 in a child with normal karyotype, resulting from malsegregation of maternal Robertsonian translocation. European Human Genetics Conference, Vienna, Austria
- Robinson WP, Wagstaff J, Bernasconi F, et al 1993. Uniparental disomy explains the occurrence of the Angelman or Prader-Willi syndrome in patients with an additional small inv dup(15) chromosome. *J Med Genet* 30:756-760.
- Robinson WP, McGillivray B, Lewis MES, Arbour L, Barrett I, Kalousek DK. 2005. Prenatally detected trisomy 20 mosaicism. *Prenat Diagn* 25:239-244.
- Ruggeri A, Dulcetti F, Miozzo M, Grati FR, Grimi B, Bellato S, Natacci F, Maggi F, Simoni G. 2004. Prenatal search for UPD14 and UPD15 in 83 cases of familial and *de novo* heterologous Robertsonian translocations. *Prenat Diagn* 24:997-1000.

Shaffer LG, Agan N, Goldberg J D, Ledbetter D H, Longshore JW, Cassidy SB. 2001. American College of Medical Genetics Statement on Diagnostic Testing for Uniparental Disomy. *Am J Med Genet*, 3:206-211.

Shaffer LG. 2006. Risk estimates for uniparental disomy following prenatal detection of a nonhomologous Robertsonian translocation. *Prenat Diag* 26:303-307.

Shield JPH, Temple IK. 2002. Neonatal diabetes mellitus. *Ped Diab* 3:109-112.

Silverstein S, Lerer I, Sagi M, Frumkin A, Ben-Neriah Z, Abeliovich D 2002. Uniparental disomy in fetuses diagnosed with balanced Robertsonian translocations: risk estimate. *Prenat Diag* 22:649-651.

Smeets DFCM, Hamel BCJ, Nelen MR, Smeets HJM, Bollen JHM, Smits APT, Ropers H-H, van Oost BA. 1992. Prader-Willi syndrome and Angelman syndrome in cousins from a family with a translocation between chromosomes 6 and 15. *N Engl J Med* 326:807-811.

Smith A, Deng Z-M, Beran R, Woodage T, Trent RJ. 1994. Familial unbalanced translocation t(8;15)(p23.3;q11) with uniparental disomy in Angelman syndrome. *Hum Genet* 93:471-473.

Tomkins DJ, Roux AF, Waye J, Freeman VC, Cox DW, Whelan DT. 1996. Maternal uniparental isodisomy of human chromosome 14 associated with a paternal t(13q14q) and precocious puberty. *Eur J Hum Genet* 4:153-159.

Webb A, Beard J, Wright C, Robson S, Wolstenholme J, Goodship J. 1995. A case of paternal uniparental disomy for chromosome 11. *Prenat Diag* 15:773-777.

Wolstenholme J, White I, Sturgiss S, Carter J, Plant N, Goodship A. 2001. Maternal uniparental heterodisomy for chromosome 2: detection through 'atypical' maternal AFP/hCG levels, with an update on a previous case. *Prenat Diagn* 21:813-817