

Uniparental Disomy (UPD)

Introduction

The 46 chromosomes in each cell of the human body can be divided into 23 pairs.¹ Normally, one chromosome of each pair is inherited from the mother and one from the father. Uniparental disomy (UPD) is an atypical inheritance pattern in which both members of a single pair of chromosomes are inherited from one parent.²

UPD is commonly initiated when chromosomes fail to separate properly during the development of an egg or sperm in meiosis. The abnormal separation is due either to nondisjunction or the presence of a chromosome translocation (fusion of one part of a chromosome onto another chromosome). Nondisjunction leads to a trisomy (an extra copy of a chromosome) or monosomy (a missing copy of a chromosome) in the conceptus. A chromosome translocation in the egg or sperm can result in a complete trisomy, a partial trisomy, or monosomy (extra or missing portions of a single chromosome) in the fertilized egg. In an attempt to regain a balanced chromosome number, a second event occurs to “rescue” this imbalance, either by loss of an extra chromosome in the trisomic cell or by the duplication of a chromosome in the monosomic cell. UPD occurs when this rescue event leaves the cell with a chromosome pair that originated from only one parent (Figure 1).²

Uniparental disomy has been reported for the majority of chromosome pairs without any definitive clinical outcome^{2,3}; however, UPD for certain chromosome pairs results in recognizable genetic conditions.² These chromosomes have genes that are imprinted. Imprinted genes are preferentially turned on (expressed) or off (not expressed) depending on which parent passes the gene to the offspring.² One example is a specific gene (*SNRPN*) on chromosome 15 involved in the Prader-Willi syndrome. The *SNRPN* gene

is expressed only when it is inherited from the father. If the father’s *SNRPN* gene is absent due to maternal UPD 15, the child will be affected with Prader-Willi syndrome.⁴ Parent-specific imprinting and consequences of UPD are known for maternal chromosomes 7, 14, and 15, and paternal chromosomes 6, 11, 14, and 15.²

Another concern with UPD is the risk for an autosomal recessive disorder,^{2,3} such as cystic fibrosis (CF). In typical Mendelian inheritance of an autosomal recessive disorder, both parents must be carriers of a disease-causing mutation for the disease to occur. UPD may result in the presence of a recessive condition when only one parent carries a mutation. In this case, a child inherits two copies of a mutation-carrying gene from a single parent. This has been documented for several genetic conditions.²

The chance that UPD exists when a trisomy, mosaicism (partial trisomy), or balanced translocation are observed in prenatal diagnosis ranges from less than 1% to approximately 66%. Due to the broad range of risk and genetic counseling issues, UPD testing should be considered in the following situations:²

- Prenatal detection of chromosomal mosaicism or complete trisomy in a chorionic villus sample (CVS) for chromosomes 6, 7, 11, 14, 15
- Prenatal detection of a balanced Robertsonian translocation involving chromosomes 14 or 15
- Individuals presenting with features consistent with disorders known to be associated with UPD²
- Fetus or symptomatic patient with a de novo supernumerary marker chromosome (SMC) identified by chromosome analysis⁵

Test Options

Testing for UPD involves DNA analysis that compares markers on a particular chromosome between the mother, father, and child (or fetus). LabCorp’s UPD test is available for all chromosomes. Since this test can reveal nonpaternity, informed consent prior to testing should be obtained.

An alternative test, requiring a sample from only the child, or fetus, is available to identify imprinting defects for chromosomes 14 and 15. This test examines a specific gene on chromosome 14 (*MEG3*) or chromosome 15 (*SNRPN*) that is imprinted (methylated) differently, depending on whether it was inherited from the mother or the father.^{6,7} The chromosome 15 methylation analysis identifies approximately 78% of cases of Angelman syndrome and more than 99% of Prader-Willi syndrome.⁸ The chromosome 14 methylation test identifies all cases of maternal UPD14 and paternal UPD 14⁶; however, it does not identify the underlying genetic mechanism, which could be an imprinting defect, deletion, or UPD.⁷

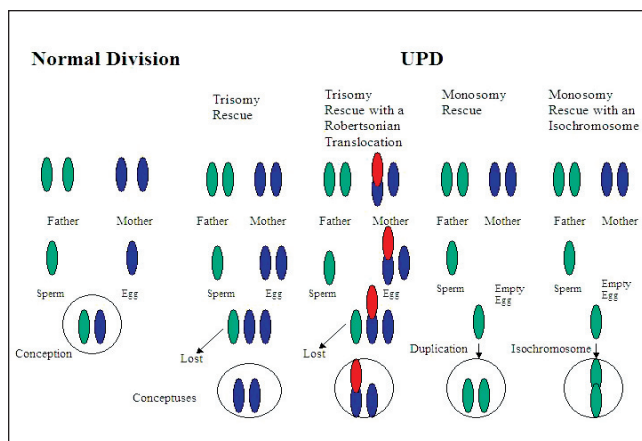


Figure 1.—Common Mechanisms Leading to UPD²

Uniparental Disomy Profile 470054

CPT 83891; 83894; 83900; 83912

Special Instructions A separate test request form must be completed for each family member submitted. The patient's name, age, and relevant clinical and family history should be included on the corresponding test request form. Please include chromosome pair to be studied. Blood specimens from both parents should be submitted, although a specimen from one parent may be sufficient in some cases.

Specimen Whole blood or amniotic fluid

Volume 7 mL whole blood or 10 mL amniotic fluid or amniocyte culture

Minimum Volume 3 mL whole blood or 5 mL amniotic fluid

Container Lavender-top (EDTA), green-top (heparin) or yellow-top (ACD) tube, sterile plastic conical tube or two confluent T-25 flasks for fetal testing

Storage Instructions Maintain specimen at room temperature. Do not freeze.

Causes for Rejection Frozen or hemolyzed specimen; improper container

Use Establish the parent of origin for syndromes that may result from single parent inheritance of both homologues of a specific chromosome pair. The best examples of this are Prader-Willi and Angelman syndromes in which maternal and paternal uniparental disomy (for chromosome 15), respectively, are reported. Other examples include Russell-Silver syndrome (chromosome 7) and Beckwith-Wiedemann syndrome (chromosome 11).

Limitations This procedure may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Analysis of VNTRs and AMPFLPs by polymerase chain reaction (PCR) and gel electrophoresis.

Angelman and Prader-Willi Syndromes, DNA Analysis

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CPT 83891; 83894; 83900; 83912

Related Information Fluorescence in situ Hybridization (FISH), Microdeletion Syndromes

Synonyms Prader-Willi and Angelman Syndromes, DNA Analysis

Special Instructions Please provide pertinent findings, family or personal, of mental retardation, autistic behaviors, developmental delay and obesity.

Specimen Whole blood, amniotic fluid or LabCorp buccal swab kit (Buccal swab collection kit contains instruction for use of a buccal swab.) **Note:** Submission of maternal blood is required for fetal testing.

Volume 7 mL whole blood, 10 mL amniotic fluid, or LabCorp buccal swab kit

Minimum Volume 3 mL whole blood, 5 mL amniotic fluid, or two buccal swabs

Container Lavender-top (EDTA) tube, yellow-top (ACD) tube, sterile plastic conical tube, or two confluent T-25 flasks for fetal testing, or LabCorp buccal swab kit

Storage Instructions Maintain specimen at room temperature or refrigerate. Do not freeze.

Causes for Rejection Frozen or hemolyzed specimen; quantity not sufficient for analysis; improper container; one buccal swab

Use This test will detect all major causes of Prader-Willi and Angelman syndrome. These include uniparental disomy (UPD), microdeletions and imprinting center defects. It is recommended that, in addition to this methylation-based test, Chromosome Analysis, High Resolution (052027) be ordered to distinguish between the underlying mechanisms.

Limitations Approximately 11% of Angelman syndrome cases arising from *UBE3A* mutations will not be detected by this test. This procedure may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Methylation-sensitive PCR and gel electrophoresis

Uniparental Disomy of Chromosome 14 (UPD 14) . . . 470060

CPT 83891; 83901; 83894; 83912

Specimen Whole blood, amniotic fluid (direct or cultured) or LabCorp buccal swab kit (The buccal swab collection kit contains instructions for use of a buccal swab.)

Volume 7 mL whole blood, 10 mL amniotic fluid, or LabCorp buccal swab kit

Minimum Volume 3 mL whole blood, 5 mL amniotic fluid, or two buccal swabs

Container Lavender-top (EDTA) tube or yellow-top (ACD) tube, sterile plastic conical tube or two confluent T-25 flasks for fetal testing, or LabCorp buccal swab kit

Storage Instructions Maintain at room temperature or refrigerate at 4°C

Causes for Rejection Hemolysis; quantity not sufficient for analysis; improper container; one buccal swab

Use Methylation-specific PCR is used to amplify divergent lengths of the methylated and unmethylated *MEG3* DMR region on chromosome 14q32 in a single reaction and thereby accurately identify the normal, maternal UPD14 and paternal UPD14 patterns.

Limitations Molecular analysis of the *MEG3* gene is performed by methylation-specific PCR and gel electrophoresis. This assay detects all cases of maternal UPD14 and paternal UPD14 arising from UPD, microdeletions, and imprinting defects but does not define the nature of underlying genetic defect. Molecular-based testing is highly accurate, but as in any laboratory test, rare diagnostic errors may occur. This procedure may be considered by Medicare and other carriers as investigational and, therefore, may not be payable as a covered benefit for patients.

Methodology Methylation-specific polymerase chain reaction and gel electrophoresis

UPD Syndromes²

Angelman Syndrome. Associated with severe mental retardation, absent speech, ataxia, seizures, paroxysmal laughter. Approximately 3% to 5% of cases result from paternal UPD 15.

Beckwith-Wiedemann Syndrome. An overgrowth syndrome associated with macroglossia, organomegaly, omphalocele, and Wilms tumor. About 20% have paternal UPD for the distal arm of chromosome 11.

Maternal UPD 14. Common features are short stature, hypotonia, hyperextensible joints, mildly dysmorphic features, developmental delay, and precocious puberty.

Paternal UPD 14. Features include mental retardation, short limb dwarfism with small thorax, respiratory difficulties, dysmorphic features, and scoliosis.

Prader-Willi Syndrome. Characterized by severe hypotonia in infancy, followed by excessive eating, obesity, cognitive impairment, behavior problems, and hypogonadism. Approximately 28% of cases are a result of maternal UPD 15.

Russell Silver Syndrome. Associated with pre- and postnatal growth retardation and dysmorphic features. About 10% of patients have maternal UPD for chromosome 7.

Transient Neonatal Diabetes Mellitus. About 20% of cases have UPD of paternal chromosome 6.

References

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3. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: Phenotype and bibliography updated. *Am J Med Genet A*. 2005 Jul; 136(3):287-305.
4. Cassidy SB, Dykens E, Williams CA. Prader-Willi and Angelman syndromes: Sister imprinted disorders. *Am J Med Genet*. 2000; 97(2):136-146.
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7. Cassidy DB, Beaudet AL, Knoll JHM, et al. ASHG/ACMG report. Diagnostic testing for Prader-Willi and Angelman syndromes. Report of the ASHG/ACMG test and technology transfer committee. *Am J Hum Genet*. 1996; 58:1085-1088.
8. GeneReviews of Angelman Syndrome. Available at: www.genetests.org. Accessed November 8, 2005.

For information regarding UPD testing, call LabCorp Genetic Services at 800-345-GENE.



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