THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Prader-Willi Syndrome Testing

Clinical Features:

Prader-Willi syndrome (PWS) [OMIM #176270] is a genetic disorder which causes hypotonia and poor feeding in infancy, followed by the development of hyperphagia and subsequent obesity. Physical characteristics of PWS also include short stature, small hands and feet, and a characteristic facial appearance consisting of a thin upper-lip, down-turned mouth, dental crowding, and almond shaped eyes. Developmental milestones are delayed, and learning disabilities are always present, but may vary in severity. Behavioral problems include temper tantrums, obsessive compulsive tendencies, and skin-picking. Psychosis occurs in 5-10% of patients as young adults (1). Individuals with PWS do not undergo spontaneous pubertal development and are infertile (1, 2).

Inheritance:

PWS is caused by the absence of paternally expressed, maternally silenced genes in the imprinted region located at 15q11-q13. This can occur by one of several mechanisms including a *de novo* paternal deletion in this region, maternal uniparental disomy (UPD), an imprinting center defect, or a paternal chromosomal translocation. Mutations in the paternal copy of the *MAGEL2* gene located at 15q11.2 have also been described in patients with classic PWS and patients with PWS-like features (3). The recurrence risk depends on the mechanism involved and may be up to 50%. PWS affects approximately 1 in 25,000 births and displays no ethnic or gender preference (2, 4).

Molecular Genetics:

- Approximately 70% of individuals with PWS have a de novo deletion of 15q11-q13 on the paternally contributed chromosome, corresponding to a less than 1% recurrence risk (2).
- Approximately 25% of PWS is due to maternal UPD15, corresponding to a less than 1% recurrence risk (2).
- 2-5% of patients have an imprinting center (IC) abnormality of which 10-40% are deletions of the IC region. A recurrence risk of up to 50% applies to the IC deletion group and a low recurrence risk of less than 1% applies to the remainder of the IC abnormality group (2).
- Less than 1% of PWS is due to a paternal chromosome 15 translocation, which may result in a recurrence risk of up to 25% (2).
- *De novo* truncating mutations in the paternally inherited copy of *MAGEL2* have been associated with classic PWS or PWS-like features (3). The proportion of PWS associated with *MAGEL2* mutations is unknown, but is predicted to be low.

Additional Resources:

Prader-Willi Syndrome Association
5700 Midnight Pass Road, Suite 6
Sarasota, FL 34242
Phone: 800-926-4797
email: national@pwsausa.org
www.pwsausa.org/index.html

Test methods:

We recommend methylation-specific (MS)-MLPA as the initial test for PWS. This testing will identify patients with abnormal methylation, large deletions and imprinting center deletions. Those patients with abnormal methylation, but no deletion, should pursue UPD testing for UPD15. For patients with normal MS-MLPA results, mutation analysis of the *MAGEL2* gene can be considered.

Methylation-specific MLPA (MS-MLPA)

Sample specifications:	3-10 cc of blood in a purple top (EDTA) tube
Cost:	$525
CPT codes:	81331
Turn-around time:	4 weeks

Microsatellite analysis for UPD15 testing

Sample specifications:	3-10 cc blood from patient and BOTH parents in purple top EDTA tubes
Cost:	$540 (total for a patient's and both parents' blood samples)
CPT codes:	81402
Turnaround time:	2 – 4 weeks

Imprinting center deletion analysis

Sample specifications:	3-10 cc of blood in a purple top (EDTA) tube
Cost:	$450
CPT codes:	81403
Turn-around time:	4 weeks

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *MAGEL2* gene is performed. Comprehensive sequence coverage of the coding regions and splice junctions of this gene is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

MAGEL2 mutation analysis

Sample specifications:	3-10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81403
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Chen C, Visootsak J, Dills S et al. Prader-Willi syndrome: an update and review for the primary pediatrician. Clin Pediatr (Phila) 2007: 46: 580-591.
2. Driscoll D, Miller J, Schwartz S et al. Prader-Willi Syndrome. In: Pagon R, Bird T, Dolan C, eds. GeneReviews [Internet]. Seattle: University of Washington, 1998.
3. Schaaf CP, Gonzalez-Garay ML, Xia F et al. Truncating mutations of MAGEL2 cause Prader-Willi phenotypes and autism. Nat Genet 2013: 45: 1405-1408.
4. Whittington JE, Holland AJ, Webb T et al. Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. J Med Genet 2001: 38: 792-798.