

# Prader-Willi Syndrome

## TO CONFIRM DIAGNOSIS OF PRADER-WILLI SYNDROME (PWS)

### Disease Overview

- Infants with PWS often have hypotonia, feeding difficulties, failure to thrive, and hypogonadism.
- Characteristics in affected children include developmental delay/mild mental retardation, hyperphagia, and rapid weight gain between 1 and 6 years of age, leading to central obesity and incomplete and delayed puberty. Common facial features include almond-shaped palpebral fissures, a downturned mouth, and a narrow bifrontal diameter.
- Affected adults often have short stature; small hands and feet; obesity; noninsulin-dependent diabetes mellitus; distinctive behavioral phenotype such as temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive behavior; and infertility (99 percent).
- Molecular confirmation of diagnosis is useful in all individuals to determine etiology, recurrence risk, and appropriate early interventions such as assisted-feeding techniques in infancy to assure adequate nutrition, physical therapy to improve hypotonia, routine eye exams to detect strabismus, and human growth hormone replacement to influence body composition.
- All individuals with PWS should be assessed for the presence of scoliosis. Adults also need to be assessed for osteoporosis. Strict food intake supervision is crucial in keeping body mass index below 30. A behavior-management program, speech as well as occupational therapy, and individual learning plans can be beneficial in achieving the individuals' full potential.
- Behavior and weight in adulthood is typically managed in group homes for individuals with PWS.

### Incidence

PWS occurs in approximately one in 15,000 live births.

### Genetics

- PWS is caused by lack of expression of the paternally contributed PWS/Angelman syndrome (AS) critical region (PWS/ASCR) on chromosome 15q11.2-q13.
- The etiology of PWS is as follows:
  - Deletion of PWS/ASCR (70–75 percent).
  - Maternal uniparental disomy for chromosome 15 (25–29 percent).
  - Imprinting center defect or balanced PWS/ASCR chromosomal translocation (< 1 percent).
  - Chromosomal rearrangement deleting the PWS/AS region (1 percent).
- Recurrence risk in siblings is dependent on the mechanism responsible for PWS in the affected child. If PWS is caused by a deletion in the PWS region, uniparental disomy, imprinting defect without mutation, or a de novo balanced translocation breaking within the PWS/ASCR, the recurrence risk is less than 1 percent. If PWS is caused by a mutation in the imprinting center

or parental translocation, the recurrence risk may approach 50 percent and 25 percent, respectively.

### Indications for Ordering

To establish a diagnosis of PWS in individuals with clinical symptoms.

### Contraindication

Prenatal diagnosis.

### Interpretation

- Absence of the paternally contributed and presence of only the maternally contributed PWS/ASCR is indicative of PWS.
- Normal methylation pattern in the PWS/ASCR reduces the risk for PWS by 99 percent.
- Methylation pattern in the PWS/ASCR that is characteristic of paternal inheritance is predictive of Angelman Syndrome.
  - An abnormal methylation result should be followed by FISH or array CGH to determine if a deletion is present. If a deletion is present, chromosome analysis should be performed to exclude a chromosome rearrangement that may alter recurrence risk.
  - If FISH analysis is normal, DNA polymorphism analysis should be performed to distinguish between maternal UPD and an imprinting defect.
  - If there is no UPD, further DNA studies can determine if an imprinting center deletion is present.
  - Parental testing may be indicated to determine if chromosomal deletions, chromosomal rearrangements, or gene mutations are de novo.

### Methodology

- Bisulfite conversion and PCR amplification of the PWS/ASCR using parent-specific, methylation-sensitive primers followed by melting-curve analysis.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity and specificity are 99 percent.

### Limitations

- Molecular mechanisms not affecting methylation patterns that may result in PWS will not be detected.
- Rare diagnostic errors can occur due to primer- or probe-site mutations.

### Related Tests

- Chromosome Analysis, FISH-Metaphase ([2002299](#))
- Chromosome Analysis, Peripheral Blood ([2002289](#))

## References

1. GeneTests. <http://www.genetests.org> (accessed on April 14, 2011).
2. Goldstone AP, et al. Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab* 2008;93(11):4183–97.
3. Goldstone AP. Prader-Willi syndrome: advances in genetics, pathophysiology and treatment. *Trends Endocrinol Metab* 2004;15(1):12–20.
4. Nativio DG. The genetics, diagnosis, and management of Prader-Willi syndrome. *J Pediatr Health Care* 2002;16(6):298–303.
5. Nolan ME. Anticipatory guidance for parents of Prader-Willi children. *Ped Nurs* 2003;29:427–30.

## Test Information

### **2005077**      **Angelman Syndrome and Prader-Willi Syndrome by Methylation**

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).