SickKids | Genome Diagnostics

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is characterized by severe muscle weakness, feeding difficulties and failure to thrive in early infancy, followed in later infancy by uncontrolled appetite and severe obesity. Patients with some degree of intellectual disability and behavioral problems are common. In addition, male PWS patients show short stature, small hands and feet and undescended testes.

Genetics

There are a number of genetic changes that cause PWS, although each produce similar clinical phenotypes. Approximately 70-75% of PWS cases are the result of a deletion of the PWS critical region of the paternal chromosome 15. Approximately 25% of cases have received two copies of chromosome 15 from their mother and none from their father, maternal uniparental disomy (matUPD). Both the deletion patients and the UPD patients are deficient for paternally derived genes in the PWS critical region. Approximately 5% of patients have an 'imprinting mutation' which alters the normal expression of paternal genes in the PWS critical region.

DNA in the PWS critical region is methylated. If the normal expression of genes in the critical region is altered due to deletion, UPD or imprinting mutations, the methylation pattern is also changed. Therefore, testing the methylation status of genes within the critical region allows these genetic alterations to be detected. For molecular analysis, the methylation status of the gene *SNRPN* within the PWS critical region is measured. Abnormal methylation of the paternally derived genes is diagnostic of Prader Willi syndrome.

Test Methods

- Quantitative testing to determine the methylation status of the *SNRPN* gene, using MLPA (Multiplex Ligation dependent Probe Amplification)

- STR analysis can be used to determine if the lack of paternal allele expression is due to maternal UPD or imprinting mutations. Highly polymorphic DNA marker alleles associated with the PWS critical region in the affected individual are compared to the pattern of markers in the parents to determine the parental origin and genetic nature of the disorder.

Test Sensitivity

Deletion, maternal UPD, and imprinting mutations account for ~99% of abnormal expression of paternal alleles in PWS cases. A very small number of PWS patients have genetic alterations other than deletion, UPD or imprinting mutations. These individuals will not be diagnosed by this analysis.

Who Should be Tested?

- Individuals clinically suspected of being affected with PWS

- Pregnancies at risk due to family history of PWS

Potential Outcomes & Interpretation of Test Results

SNRPN Methylation Status	Explanation
Normal methylation	This result does not support a diagnosis of PWS
Abnormal methylation	This result supports a diagnosis of PWS
Deletion detected	This result supports a diagnosis of PWS

For More Information

Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/omim/ Item # 176270

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pws

Canadian Prader-Willi Syndrome Organization http://www.geocities.com/cpwso/cpwso.html

Prader-Willi Syndrome Association (USA) http://www.pwsausa.org/

To locate a genetics center near you, visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Rare cases of PWS result from a subtle genetic rearrangement involving one of the parents. These will not be detected by the procedures used in the Molecular Genetics Laboratory. Identification of these cases can be done by cytogenetic analysis.

2. A negative molecular test result does not rule out a clinical diagnosis of PWS. PWS may be caused by point mutations or small deletions in the PWS critical region that are not detected by the diagnostic procedures used.

3. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.