Angelman Syndrome and Prader-Willi Syndrome Testing

Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are complex neurodevelopmental disorders characterized by developmental delay and intellectual disability, as well as symptoms unique to each disorder (e.g., unique happy demeanor in AS, excessive eating in PWS). Both conditions are linked to loss of function of genes in the 15q11.2-q13 region.

DISEASE OVERVIEW

Prevalence
- AS: one in 12,000-24,000
- PWS: one in 10,000-30,000

Age of Onset
- AS: 6-12 months
- PWS: Neonatal

For more information about the clinical characteristics of AS and PWS, see the Angelman Syndrome and Prader-Willi Syndrome Consult topic.

GENETICS

Genes
15q11.2-q13 region

Etiologies
- Deletion of 15q11.2-q13 (AS: maternal; PWS: paternal)
- Uniparental disomy (UPD) for chromosome 15 (AS: paternal; PWS: maternal)
- UBE3A gene mutation (AS only)
- Imprinting center defect
- Unbalanced chromosome translocation
- Unidentified (AS only)

For more information about the underlying mechanisms of AS and PWS, see the Angelman Syndrome and Prader-Willi Syndrome Consult topic.

Prenatal Screening
- Prenatal testing is recommended for subsequent pregnancies of couples who have a previous child with AS or PWS
- Parental testing does not exclude somatic and/or germline mosaicism
- Methylation testing is not offered on chorionic villus samples
- Incomplete methylation in early embryonic development may cause false-positive results

TEST INTERPRETATION

<table>
<thead>
<tr>
<th>DNA Methylation</th>
<th>UBE3A Gene Sequencing</th>
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<tbody>
<tr>
<td>Clinical sensitivity</td>
<td>AS: ~80%</td>
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<tr>
<td></td>
<td>PWS: &gt;99%</td>
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TESTS TO CONSIDER

Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR 2005077
Method: Methylation Sensitive Polymerase Chain Reaction/Fluorescence Monitoring
Preferred initial diagnostic test for AS or PWS
Establish diagnosis in individuals with clinical symptoms

Angelman Syndrome (UBE3A) Sequencing 2005564
Method: Polymerase Chain Reaction/Sequencing
Second-tier test for the diagnosis of AS
Order if suspicion for AS remains after normal methylation analysis
Establish diagnosis in individuals with clinical symptoms of AS and normal DNA methylation

Chromosome FISH, Metaphase 2002299
Method: Fluorescence in situ Hybridization
Follow-up for abnormal methylation test for AS

Cytogenomic SNP Microarray 2003414
Method: Genomic Microarray (Oligo-SNP Array)
Follow-up for abnormal methylation test for AS
<table>
<thead>
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<th>DNA Methylation</th>
<th>UBE3A Gene Sequencing</th>
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<tr>
<td><strong>Analytical sensitivity</strong></td>
<td>99%</td>
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<tr>
<td><strong>Positive result</strong></td>
<td>Confirms diagnosis of AS in symptomatic individual</td>
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<td>Absence of appropriate methylated parental allele confirms diagnosis</td>
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<td>Follow-up with fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (CGH) to determine whether deletion is present</td>
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<tr>
<td>- If large deletion is present</td>
<td>Order chromosome analysis in parent to exclude rearrangement (alters recurrence risk; see AS and PWS Consult topic)</td>
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<tr>
<td>- If FISH is normal</td>
<td>Order DNA polymorphism analysis to distinguish between UPD and imprinting defect</td>
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<tr>
<td>- If no UPD</td>
<td>Order further DNA studies to detect imprinting defect</td>
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<tr>
<td>Testing of both parents may be necessary</td>
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<tr>
<td><strong>Inconclusive result</strong></td>
<td>Gene variant detected, but whether the variant is benign or pathogenic is unclear</td>
</tr>
<tr>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>Regulatory mutations, deep intronic mutations, and large deletions/duplications will not be detected</td>
</tr>
<tr>
<td>Specific molecular mechanism responsible for abnormal methylation results cannot be determined via this test alone</td>
<td>Diagnostic errors may occur due to rare sequence variations</td>
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<tr>
<td>AS or PWS resulting from molecular mechanisms that do not affect methylation patterns will not be identified</td>
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<td>Diagnostic errors can occur due to rare sequence variations</td>
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</table>

**REFERENCES**


RELATED INFORMATION

Angelman Syndrome and Prader-Willi Syndrome
Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder Laboratory Testing - Neurocognitive Impairments Testing for Genetic Syndromes Related to Developmental Delay (DD), Intellectual Disability (ID), and Autism Spectrum Disorder (ASD)

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology.
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