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 (eg, 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

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
- Use to establish a 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
- Use to establish a diagnosis in individuals with clinical symptoms of AS and normal DNA methylation

Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR, Fetal 2012232

Method: Methylation Sensitive Polymerase Chain Reaction/Fluorescence Monitoring

- Prenatal testing for AS or PWS
- Use to identify cases resulting from molecular mechanisms that produce abnormal methylation patterns

Chromosome FISH, Metaphase 2002299

Method: Fluorescence in situ Hybridization (FISH)

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

Rett Syndrome (MECP2), Sequencing and Deletion/Duplication 0051614

Method: Sequencing/Multiplex Ligation-dependent Probe Amplification

Rule out an *MECP2* gene mutation in individuals with clinical features of AS who lack a molecular abnormality involving 15q11.2-q13

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

Useful when a pathogenic familial variant identifiable by sequencing is known.

Test Interpretation

	DNA Methylation	*UBE3A* Gene Sequencing
Clinical sensitivity	AS: ~80% PWS: >99%	AS: 11% PWS: n/a
Analytical sensitivity	99%	99%

Positive result	Absence of appropriate methylated parental allele confirms diagnosis
	Follow-up with fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (CGH) to determine whether deletion is present
	• If large deletion is present
	  ◦ Order chromosome analysis in parent to exclude rearrangement (alters recurrence risk; see AS and PWS Consult topic)
	• If FISH is normal
	  ◦ Order DNA polymorphism analysis to distinguish between UPD and imprinting defect
	• If no UPD
	  ◦ Order further DNA studies to detect imprinting defect
	Testing of both parents may be necessary
		Confirms diagnosis of AS in symptomatic individual

Inconclusive result	n/a	Gene variant detected, but whether the variant is benign or pathogenic is unclear
Limitations	Specific molecular mechanism responsible for abnormal methylation results cannot be determined via this test alone AS or PWS resulting from molecular mechanisms that do not affect methylation patterns will not be identified Diagnostic errors can occur due to rare sequence variations	Regulatory mutations, deep intronic mutations, and large deletions/duplications will not be detected Diagnostic errors may occur due to rare sequence variations

n/a, not applicable

Additional Resources

Dagli AI, Mueller J, Williams CA. Angelman syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. GeneReviews, University of Washington; 1993-2020. [Last Revision: Dec 2017; Accessed: Sep 2020]

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Driscoll DJ, Miller JL, Schwartz S, et al. Prader-Willi syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Dec 2017; Accessed: Sep 2020]

Goldstone AP, Holland AJ, Hauffa BP, et al. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab. 2008;93(11):4183-4197. PubMed

Beygo J, Buiting K, Ramsden SC, Ellis R, Clayton-Smith J, Kanber D. Update of the EMQN/ACGS best practice guidelines for molecular analysis of Prader-Willi and Angelman syndromes. Eur J Hum Genet. 2019;27(9):1326-1340. PubMed

Related Information

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

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Content Review September 2020 | Last Update September 2020