Angelman Syndrome and Prader-Willi Syndrome by Methylation-Specific MLPA

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Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are complex neurodevelopmental disorders characterized by developmental delay and cognitive 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.

Featured ARUP Testing

Angelman Syndrome and Prader-Willi Syndrome by Methylation-Specific MLPA 3006247

Method: Qualitative /Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA)

- Preferred initial diagnostic test for AS or PWS
- Use to establish a diagnosis in individuals with clinical symptoms
- Prenatal testing for AS or PWS to identify cases resulting from molecular mechanisms that produce abnormal methylation patterns

Disease Overview

Prevalence

- AS: 1 in 12,000-24,000[1,2]
- PWS: 1 in 10,000-30,000[1,2]

Age of Onset

- AS: 6-12 months of age[1,2]
- PWS: Neonatal[1,2]

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)
- Imprinting center defect
- Unbalanced chromosome translocation
- *UBE3A* gene mutation (AS only)
- Unidentified (AS only)

For more information about the underlying mechanisms of AS and PWS, refer to the ARUP Consult Angelman Syndrome and Prader-Willi Syndrome 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.
- Testing of chorionic villus samples is not recommended as methylation may be incomplete in early embryonic development.

Test Interpretation

Clinical Sensitivity

- >99% for PWS[2]
- 80% for AS[1]

Analytic Sensitivity

99% for PWS and AS

Results

Positive Result	
Finding	**Interpretation**
Maternally contributed AS/PWS critical region only, with normal copy number	• Confirms a diagnosis of PWS • Order DNA polymorphism analysis to distinguish between UPD and imprinting defect
Maternally contributed AS/PWS critical region only, with abnormal copy number consistent with deletion	• Confirms a diagnosis of PWS • Consider chromosome analysis for proband to exclude rare rearrangement and to determine the need for paternal/maternal karyotyping[a]
Paternally contributed AS/PWS critical region only, with normal copy number	• Confirms a diagnosis of AS • Order DNA polymorphism analysis to distinguish between UPD and imprinting defect
Paternally contributed AS/PWS critical region only, with abnormal copy number consistent with deletion	• Confirms a diagnosis of AS • Consider both chromosome analysis and fluorescence in situ hybridization (FISH) in mother to exclude rare rearrangement[a]
Paternally and maternally contributed AS/PWS critical regions detected, with abnormal copy number consistent with duplication	This assay is not validated to detect increased copy number of 15q11.2-q13 or determine parent of origin for duplications

[a]Alters recurrence risk. Refer to the ARUP Consult Angelman Syndrome and Prader-Willi Syndrome topic for more information.

Negative Result	
Finding	**Interpretation**
Normal methylation pattern of both maternally and paternally contributed AS/PWS critical regions with normal copy number	• Greatly reduces the probability of a PWS diagnosis; <1% of individuals with PWS have normal methylation patterns • Reduces, but does not exclude, the probability of an AS diagnosis; approximately 20% of individuals with AS have normal methylation patterns

Limitations

- Disease mechanisms causing AS that do not alter methylation patterns will not be detected.
- The specific molecular mechanism responsible for abnormal methylation results cannot be determined via this test alone.
- Diagnostic errors can occur due to rare sequence variations.
- This assay is not validated to detect increased copy number of 15q11.2-q13 or determine parent of origin for duplications.
- This assay cannot distinguish between UPD and imprinting defects causative of PWS and AS.
- AS and PWS mosaicism will not be assessed by this assay.
- Interpretation of this test result may be impacted if the proband has had an allogeneic stem cell transplantation.
- Methylation patterns may not be fully established in early gestation; thus, diagnostic testing on chorionic villus samples is not recommended.

References

1. Dagli AI, Matthews J, Williams CA. Angelman syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Updated Apr 2021; accessed Mar 2023.

2. Driscoll DJ, Miller JL, Cassidy SB, et al. Prader-Willi syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Updated Mar 2023; accessed Mar 2023.

Additional Resources

Beygo J, Buiting K, Ramsden SC, et al. 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.

Diagnostic testing for Prader-Willi and Angelman syndromes: report of the ASHG/ACMG Test and Technology Transfer Committee. *Am J Hum Genet*. 1996;58(5):1085-1088.

Goldstone AP, Holland AJ, Hauffa BP, et al. Recommendations for the diagnosis and management of Prader-Willi syndrome [published correction appears in *J Clin Endocrinol Metab*. 2010;95(12):5465]. *J Clin Endocrinol Metab*. 2008;93(11):4183-4197.

Related Information

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

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com