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, as well as symptoms unique to each disorder (eg, distinctive happy demeanor in AS, hyperphagia in PWS).[1,2] Both conditions are linked to loss of function of genes in the 15q11.2-q13 region.[1,2]

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

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.
- 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 Jul 2024.

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 Jul 2024.