Angelman Syndrome

Indications for Ordering

Angelman syndrome (AS) and Prader-Willi syndrome (PWS) by methylation
- Establish diagnosis in individuals with clinical symptoms

UBE3A gene sequencing
- Establish diagnosis in individuals with clinical symptoms of AS and normal DNA methylation

Test Description

DNA methylation
- Methylation sensitive polymerase chain reaction/fluorescence monitoring

UBE3A sequencing
- Bidirectional sequencing of entire *UBE3A* coding region and intron/exon borders

Tests to Consider

Primary tests

Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR 2005077
- Preferred initial diagnostic test for AS or PWS

Angelman Syndrome (*UBE3A*) Sequencing 2005564
- Second-tier test for the diagnosis of AS
- Order if suspicion for AS remains after normal methylation analysis

Related tests

Angelman Syndrome and Prader-Willi Syndrome by Methylation-Sensitive PCR, Fetal 2012232
- Prenatal testing for AS or PWS
- Identifies cases resulting from molecular mechanisms that produce abnormal methylation patterns

Chromosome FISH, Metaphase 2002299
- Follow-up for abnormal methylation test for AS

Cytogenomic SNP Microarray 2003414
- Follow-up for abnormal methylation test for AS

Rett Syndrome (*MECP2*), Sequencing and Deletion/Duplication 0051614
- 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
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence – 1/15,000

Age of onset – 6-12 months

Symptoms
- Normal development until initial symptoms – oral-motor incoordination and feeding difficulty
- Severe developmental delay
- Severe speech impairment (little or no expressive language)
- Gait ataxia/tremulousness of limbs
- Unique behaviors – eg, overly happy
- Secondary microcephaly (by age 2)
- Seizures (by age 3)
- Sleep disturbances
- Characteristic EEG pattern
- Autistic spectrum features
- Dysmorphic features – flat occiput, wide mouth, protruding tongue, prognathism, strabismus
- Hypopigmentation of skin, eyes, hair

Genetics

Gene – *UBE3A*
- Other molecular mechanisms

Inheritance – altered/inactivated/disrupted or absent maternally imprinted *UBE3A*

De novo mutations – 70-90%

Etiologies
- Maternal deletion of 15q11.2-q13 (70-90%)
- Paternal uniparental disomy (UPD) for chromosome 15 (3-7%)
- *UBE3A* gene mutation (11%)
- Imprinting center defect (2-4%)
- Unbalanced chromosome translocation (<1%)
- Unidentified (10%)

Prenatal screening

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

Test Interpretation

See table

Reference

Lossie AC, Whitney MM, et al. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. J Med Genet. 2001;38:834-835

	DNA Methylation	***UBE3A* Gene Sequencing**
Clinical sensitivity	78% (Lossie, 2001)	11% (Lossie, 2001)
Analytical sensitivity	99%	99%
Positive result	• Absence of methylated maternal allele confirms AS • Follow-up with fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (CGH) determines whether deletion is present ○ If large deletion is present ▪ Order chromosome analysis in mother to exclude rearrangement (alters recurrence risk) ○ 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 • Paternal testing may be necessary	Confirms diagnosis 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 • AS 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