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 (CVS)
  - Incomplete methylation in early embryonic development may cause false-positive results

Test Interpretation

See table

Reference


<table>
<thead>
<tr>
<th>DNA Methylation</th>
<th>UBE3A Gene Sequencing</th>
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<tbody>
<tr>
<td><strong>Clinical sensitivity</strong></td>
<td>78% (Lossie, 2001)</td>
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<tr>
<td><strong>Analytical sensitivity</strong></td>
<td>99%</td>
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**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

**Inconclusive result**

- N/A

**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

**UBE3A Gene Sequencing**

- Regulatory mutations, deep intronic mutations, and large deletions/duplications will not be detected
- Diagnostic errors may occur due to rare sequence variations

**Gene variant detected, but whether the variant is benign or pathogenic is unclear**