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


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<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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<td><strong>Positive result</strong></td>
<td>Absence of methylated maternal allele confirms AS</td>
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<td>Follow-up with fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (CGH) determines whether deletion is present</td>
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<td>- If large deletion is present</td>
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<tr>
<td><strong>Inconclusive result</strong></td>
<td>N/A</td>
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<tr>
<td><strong>Limitations</strong></td>
<td>Specific molecular mechanism responsible for abnormal methylation results cannot be determined</td>
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<td></td>
<td>AS resulting from molecular mechanisms that do not affect methylation patterns will not be identified</td>
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