Angelman Syndrome Genetic Testing

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Angelman syndrome (AS) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Chromosomal microarray [BAC], constitutional	81228
Chromosomal microarray [CGH], constitutional	S3870
Chromosomal microarray [SNP], constitutional	81229
Chromosome 15 uniparental disomy	81402
Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis	81349
FISH analysis for 15q11-q13 deletion	88271
Imprinting center defect analysis	81479
Imprinting center known familial mutation analysis	81403
SNRPN/UBE3A methylation analysis	81331
UBE3A deletion/duplication analysis	81479

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Procedures addressed by this guideline	Procedure codes
UBE3A known familial mutation analysis	81403
UBE3A sequencing	81406

Criteria

Requests for Angelman syndrome (AS) genetic testing are reviewed using the following criteria.

Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous UBE3A sequencing or imprinting center defect analysis testing that would detect the familial mutation, AND
- Family History:
  - Known familial UBE3A mutation in a blood relative, or
  - Known familial imprinting center defect mutation in a blood relative, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

SNRPN/UBE3A Methylation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous SNRPN/UBE3A methylation analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Developmental delay by age 6-12 months, typically severe to profound, without loss of milestones, and
  - Some combination of the following:
    - Movement or balance disorder, typically with ataxia, or

    - Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements),or hypermotoric behavior, or
    - Speech impairment with no or minimal number of words, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Deletion Analysis (FISH for 15q11-q13 Deletion or Chromosomal Microarray)

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - No previous chromosomal microarray, and
    - No previous 15q11-q13 deletion analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Developmental delay by age 6-12 months, typically severe to profound, without loss of milestones, and
    - Some combination of the following:
        - Movement or balance disorder, typically with ataxia, or
        - Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements),or hypermotoric behavior, or
        - Speech impairment with no or minimal number of words, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Chromosome 15 Uniparental Disomy (UPD)

- Genetic Counseling:
    - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
    - SNRPN/UBE3A methylation analysis results are abnormal, and
    - 15q11-q13 deletion analysis is negative, and
    - No previous chromosome 15 UPD studies, AND
- Diagnostic Testing for Symptomatic Individuals:
    - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Imprinting Center Defect Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are abnormal, and
  - 15q11-q13 deletion analysis is negative, and
  - Previous chromosome 15 UPD testing is negative, and
  - No previous imprinting center (IC) analysis, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

UBE3A Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are normal, and
  - No previous sequencing of UBE3A, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

UBE3A Deletion/Duplication Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - SNRPN/UBE3A methylation analysis results are normal, and
  - Normal UBE3A sequencing, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Meets clinical criteria for SNRPN/UBE3A methylation analysis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is Angelman syndrome?

Angelman syndrome (AS) is a genetic disorder that can cause intellectual disability, severe speech impairment, tremors, seizures, microcephaly, and decreased need for sleep.

Prevalence

The prevalence of AS in the population is one in 12,000-24,000.[1]

Symptoms

Clinical features of AS (quoted directly):[2]

A. Consistent (100%)

- Developmental delay, functionally severe
- Movement or balance disorder, usually ataxia of gait, and/or tremulous movement of limbs. Movement disorder can be mild. May not appear as frank ataxia but can be forward lurching, unsteadiness, clumsiness, or quick, jerky motions
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with uplifted hand-flapping, or waving movements; hypermotoric behavior
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones

B. Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (2 SD of normal OFC) by age 2 years. Microcephaly is more pronounced in those with 15q11.2-q13 deletions
- Seizures, onset usually <3 years of age. Seizure severity usually decreases with age but the seizure disorder lasts throughout adulthood
- Abnormal EEG, with a characteristic pattern, as mentioned in the text. The EEG abnormalities can occur in the first 2 years of life and can precede clinical features, and are often not correlated to clinical seizure events

C. Associated (20%-80%)

- Flat occiput
- Occipital groove
- Protruding tongue
- Tongue thrusting; suck/swallowing disorders
- Feeding problems and/or truncal hypotonia during infancy
- Prognathia
- Wide mouth, wide-spaced teeth
- Frequent drooling

- Excessive chewing/mouthing behaviors
- Strabismus
- Hypopigmented skin, light hair, and eye color compared to family, seen only in deletion cases
- Hyperactive lower extremity deep tendon reflexes
- Uplifted, flexed arm position especially during ambulation
- Wide-based gait with pronated or valgus-position ankles
- Increased sensitivity to heat
- Abnormal sleep-wake cycles and diminished need for sleep
- Attraction to/fascination with water, fascination with crinkly items such as certain papers and plastics
- Abnormal food related behaviors
- Obesity (in older child)
- Scoliosis
- Constipation

Causes

Angelman syndrome is caused by a missing or defective UBE3A gene inherited from the individual's mother.[3]

A missing or defective UBE3A gene can be caused by a gene deletion, gene mutation, uniparental disomy (two copies of the paternal chromosome), imprinting defect, or a chromosome rearrangement.[3,4]

Molecular genetic testing will identify an etiology in approximately 90% of individuals. A portion of individuals (around 10%) with a clinical diagnosis of AS will not have a molecular cause identified.[1]

Diagnosis

The diagnosis of AS is established in an individual who has findings on molecular genetic testing that are consistent with deficient expression or function of the maternally inherited UBE3A allele.[1,2,5,6]

Genetic testing is recommended when an individual has all of the clinical findings in sub-bullets A and B listed above under "symptoms" and whose developmental history is as follows:[2]

- Unremarkable prenatal and birth history. The neonate does not present with an abnormal head circumference or major birth defects although feeding difficulties may be evident.

- At 6-12 months of age, developmental delays become evident and there may be low muscle tone of the trunk. Differences in limb movements and/or increased smiling may be noticed.
- There is no regression but there is delayed development in progression of skills.
- Metabolic, hematologic, and chemistry profiles are normal.
- Overall normal brain MRI or CT although there may be "mild cortical atrophy or dysmyelination".
- The authors note that "these findings are useful as inclusion criteria but deviations should not exclude diagnosis"

Determination of recurrence risk following a diagnosis of AS may require genetic testing of one or both parents depending on the identified molecular cause.[5,6]

Management

“Anti-seizure medication for seizures. Accommodation for hypermotoric behaviors and disruptive nighttime wakefulness. Behavior modification can be effective for disruptive or self-injurious behaviors. Physical therapy, occupational therapy, and speech therapy with an emphasis on nonverbal methods of communication, including augmentative communication aids (e.g., picture cards, communication boards) and signing. Individualization and flexibility in school settings. Routine management of gastroesophageal reflux, feeding difficulties, constipation, and strabismus. Thoraco-lumbar jackets and/or surgical intervention for scoliosis. Bracing or surgery as needed for subluxed or pronated ankles or tight Achilles tendons."[1]

Other recommendations include the following:

- Sleep disturbance: Sleep concerns may require consideration of effect on other aspects of the individual's health, etiological investigations, behavioral interventions, medication trials, and evaluation by a sleep specialist.[6]
- "Surveillance: Evaluation of older children for obesity associated with an excessive appetite. Annual clinical examination for scoliosis; ophthalmology examination in the first year if strabismus is present; ophthalmology exam at age two years with follow up per ophthalmologist; clinical examination for scoliosis annually."[1]
- "Agents/circumstances to avoid: Overtreatment with sedating medications in order to reduce hyperexcitable and hypermotoric behavior. Overtreatment with antiepileptic drugs when movement abnormalities are mistaken for seizures and/or when EEG abnormalities persist even as seizures are controlled."[1]

Test information

Testing for AS may include known familial mutation analysis, SNRPN/UBE3A methylation analysis, chromosomal microarray, FISH analysis for 15q11-q13 deletion,

chromosome 15 uniparental disomy (UPD), imprinting center defect analysis, or UBE3A sequencing and deletion testing.

Known Familial Mutation Analysis: Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing. Analysis for known familial mutations typically includes only the specific mutation identified in the family, but if available, a targeted mutation panel that includes the familial mutation(s) may be performed.

SNRPN/UBE3A Methylation Analysis: This test is typically the first test in the evaluation of both Angelman syndrome (AS) and Prader-Willi syndrome (PWS). It will detect about 80% of individuals with AS and greater than 99% of individuals with PWS. However, DNA methylation analysis does not identify the underlying cause, which is important for determining the risk to future siblings. This risk ranges from less than 1% to up to 50%, depending on the genetic mechanism. Follow-up testing for these causes may be appropriate.

Chromosomal Microarray or FISH Analysis for 15q11-q13 Deletion: If DNA methylation analysis for AS or PWS is abnormal, deletion analysis is typically the next step. Approximately 70% of cases of both AS and PWS have a deletion in one copy of chromosome 15 involving the 15q11.2-q13 region. FISH (fluorescence in situ hybridization) analysis and chromosomal microarray (CMA, array CGH) can detect such deletions. If CMA has already been done, FISH is not likely to be necessary.

Chromosome 15 Uniparental Disomy (UPD): If DNA methylation analysis is abnormal but deletion analysis is normal, UPD analysis may be an appropriate next step for evaluation of both AS and PWS. About 28% of PWS cases are due to maternal UPD (both chromosome 15s are inherited from the mother). About 7% of cases of AS are due to paternal UPD (both chromosome 15s are inherited from the father). Both parents must be tested to diagnose UPD.

Imprinting Center Defect Analysis: This test may be considered in the evaluation of AS and PWS when methylation is abnormal, but FISH (or array CGH) and UPD studies are normal. Individuals with such results are presumed to have an imprinting defect. An abnormality in the imprinting process has been described in a minority of cases. However, imprinting center deletions may be familial, and if familial, the recurrence risk can be up to 50%.

UBE3A Sequencing

If DNA methylation analysis is normal, UBE3A gene mutations should be suspected. Such mutations are found in 11% of individuals with AS and can only be detected by sequencing the entire gene.[1] These mutations can be carried by the mother of an affected individual and pose up to a 50% risk of recurrence in her other children, and an increased risk to other family members.

UBE3A Gene-Targeted Deletion/Duplication Analysis

"Gene-targeted deletion/duplication analysis detects deletions or duplications in intragenic or other targeted regions. … CMA usually detects large 15q11.2-q13 deletions, but in rare instances has detected UBE3A multiexon or whole-gene deletions."[1]

Guidelines and evidence

The Angelman Syndrome Foundation

The Angelman Syndrome Foundation (ASF, 2024) recommended the following genetic testing strategy:[4,7]

- UBE3A methylation analysis
  - If normal, consider UBE3A gene sequencing.
  - If abnormal (only paternal alleles are present), a diagnosis of AS is confirmed. Consider the following to identify the underlying molecular cause for recurrence risk counseling.
- Deletion analysis (chromosomal microarray or FISH for 15q11-q13)
  - If deletion testing is abnormal, FISH testing on the mother should be done to rule out an inherited chromosome abnormality (rare).
  - If deletion testing is normal, consider UPD analysis.
- Uniparental Disomy (UPD) analysis of chromosome 15 to determine whether the proband inherited both copies of chromosome 15 from the father.
- If deletion analysis and UPD analysis are normal, an imprinting center mutation is a likely cause and should be evaluated (which may carry a higher recurrence risk than other causes).

Selected Relevant Publications

An expert-authored review (2021) commented on the appropriate diagnostic testing strategy and the utility of familial testing analysis:[1]

Diagnostic Testing:

- DNA methylation testing is usually the first-tier test. If methylation analysis is abnormal, additional analysis is needed to identify the molecular cause.
- If methylation analysis is normal, UBE3A sequencing should be considered, followed by deletion/duplication analysis.

Familial Testing:

- Individuals with an imprinting center (IC) deletion can have a phenotypically normal mother who also has an IC deletion. If a proband's mother has a known IC deletion, the risk to the sibs is 50%.

- UBE3A pathogenic variants can be inherited or de novo. Cases of somatic and germline mosaicism for a UBE3A pathogenic variant have been noted. If a proband's mother has a UBE3A pathogenic variant, the risk to the sibs is 50%.
- "If a proband's mother is heterozygous for a known imprinting center deletion or UBE3A pathogenic variant, the mother's sibs are also at risk of having the imprinting center deletion or the UBE3A pathogenic variant. Each child of the unaffected heterozygous sister is at a 50% risk of having AS. Unaffected maternal uncles of the proband who are heterozygous are not at risk of having affected children, but are at risk of having affected grandchildren through their unaffected daughters who inherited the imprinting center deletion or UBE3A pathogenic variant from them."

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Angelman Syndrome testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

1. Dagli AI, Mathews J, Williams CA. Angelman Syndrome. September 15, 1998 [Updated April 22, 2021]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: **https://www.ncbi.nlm.nih.gov/books/NBK1144** .
2. Williams CA, Beaudet AL, Clayton-Smith J, et al. Angelman syndrome 2005: updated consensus for diagnostic criteria. *Am J Med Genet* A. 2006;140(5):413-418. doi: 10.1002/ajmg.a.31074
3. Jiang Y, Lev-Lehman E, Bressler J, et al. Genetics of Angelman syndrome. *Am J Hum Genet*. 1999;65(1):1-6. doi: 10.1086/302473
4. Angelman Syndrome Foundation. Genetics of AS. Updated 2024 Available at: **https://www.angelman.org/what-is-as/genetics-of-angelman-syndrome**
5. 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. doi: 10.1038/s41431-019-0435-0.
6. Duis J, Nespeca M, Summers J, et al. A multidisciplinary approach and consensus statement to establish standards of care for Angelman syndrome. *Mol Genet Genomic Med*. 2022;10(3):e1843. doi: 10.1002/mgg3.1843
7. Angelman Syndrome Foundation. Testing and Diagnosis. Updated 2024 Available at: **https://www.angelman.org/what-is-as/testing-and-diagnosis/**