Angelman Syndrome Testing

Introduction

Angelman syndrome 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.

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What is Angelman syndrome

Definition

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

Angelman syndrome (AS) is characterized by: \(^1\)

- Severe developmental delay or intellectual disability by age 6-12 months
- Severe speech impairment — usually with minimal or no word use
- Gait ataxia and limb tremors
- Seizures and microcephaly
- Happy demeanor with hand flapping, and
- Decreased need for sleep.

Causes

Features of Angelman syndrome are caused by a missing or defective UBE3A gene inherited from the individual's mother.\(^2\)

A missing or defective UBE3A gene can be caused by a gene deletion, gene mutation, uniparental disomy (two copies of paternal chromosome), imprinting defect, or a chromosome rearrangement.\(^2,3\)

Test information

Introduction

Testing for Angelman syndrome may include SNRPN/UBE3A methylation analysis, FISH analysis for 15q11-q13 deletion, chromosome 15 uniparental disomy (UPD), imprinting center defect analysis, UBE3A sequencing, or known familial mutation analysis.

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 patients with AS and >99% of patients 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 Angelman (AS) or Prader-Willi syndrome (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. When looking specifically for this deletion, FISH (fluorescence in situ hybridization) analysis is most commonly performed. However, chromosome
microarray can also detect such deletions (see that guideline for guidance). If chromosomal microarray (CMA, array CGH) 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 Angelman (AS) and Prader-Willi syndrome (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 Angelman syndrome (AS) and Prader-Willi syndrome (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 Angelman syndrome patients 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.

Known familial mutation analysis

If a UBE3A gene mutation has been identified in an affected individual through sequencing, testing for just the known familial mutation in UBE3A can be performed for at-risk relatives, including at-risk pregnancies.

If a mutation in the imprinting center has been identified in an affected family member, testing for just the known familial mutation in the imprinting center can be performed for at-risk relatives, including at-risk pregnancies.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to Angelman syndrome testing.
The Angelman Syndrome Foundation

The Angelman Syndrome Foundation (2015) recommends the following test strategy to diagnose Angelman syndrome:

- **UBE3A methylation analysis**
  - If abnormal (only paternal alleles are present), a diagnosis is confirmed.
  - Consider the following to identify the underlying 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).

**Expert-authored review**

An expert-authored review (2011) comments on the utility of familial mutation analysis:

- “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 mutations can be inherited or de novo. In addition, several cases of mosaicism for a UBE3A mutation have been noted. If a proband's mother has a UBE3A mutation, the risk to the sibs is 50%.”

- “If a proband's mother carries a known IC deletion or UBE3A mutation, the mother's sisters are also at risk of carrying the IC deletion or the mutation. Each child of the unaffected sisters who are carriers is at a 50% risk of having AS. Unaffected maternal uncles of the proband who are carriers are not at risk of having affected children, but are at risk of having affected grandchildren through their unaffected daughters who have inherited the IC deletion or UBE3A mutation from them.”
Criteria

Introduction

Requests for Angelman syndrome testing are reviewed using these criteria.

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**

- 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:
  - 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.

**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
  o Previous chromosome 15 UPD testing is negative, and
  o No previous imprinting center (IC) analysis, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay by age 6-12 months, typically severe to profound, without
    loss of milestones, and
  o 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.

**UBE3A Sequencing**

• Genetic Counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by
    the Health Plan policy), AND

• Previous Testing:
  o SNRPN/UBE3A methylation analysis results are normal, and
  o No previous sequencing of UBE3A, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Developmental delay by age 6-12 months, typically severe to profound, without
    loss of milestones, and
  o Movement or balance disorder, typically with ataxia, and
  o Frequent laughter/smiling, apparent happy demeanor; easily excitable
    personality (often with uplifted hand-flapping, or waving movements), or
    hypermotoric behavior, and
  o Speech impairment with no or minimal number of words, 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:
  - Developmental delay by age 6-12 months, typically severe to profound, without loss of milestones, and
  - Movement or balance disorder, typically with ataxia, and
  - Frequent laughter/smiling, apparent happy demeanor; easily excitable personality (often with uplifted hand-flapping, or waving movements), or hypermotoric behavior, and
  - Speech impairment with no or minimal number of words, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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, 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.
References

Introduction

These references are cited in this guideline.

