Test Definition: UBE3Z

UBE3A Gene, Full Gene Analysis

Overview

Useful For

Confirmation of a diagnosis of Angelman syndrome in patients who have previously tested negative by methylation analysis

Genetics Test Information

Testing includes full gene sequencing of the *UBE3A* gene

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Testing Algorithm

If skin biopsy is received, fibroblast culture will be added and charged separately.

See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

Specimen preferred to arrive within 96 hours of draw.

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Submit only 1 of the following specimens:

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Specimen Stability Information: Ambient (preferred)/Refrigerated/Frozen

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask

Specimen Volume: 1 Full T-75 or 2 full T-25 flasks

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours

Specimen Type: Skin biopsy

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes can be supplied upon request (Eagle's minimum essential medium with 1% penicillin and streptomycin [T115]).

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions.

Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical and Interpretive

Clinical Information

Angelman syndrome (AS) is characterized by significant developmental delay and mental retardation, ataxia, jerky arm movements, unprovoked laughter, seizures, and virtual absence of speech. AS has several known genetic causes.

About 65% to 80% of affected individuals have a de novo deletion of essentially the same region of chromosome 15 detected for Prader-Willi syndrome (PWS): 15q11.2-13. The deletion can often be identified by high-resolution chromosome analysis in conjunction with FISH analysis. Molecular testing has shown that the AS deletion occurs only on the copy of chromosome 15 inherited from the mother. In about 5% of patients with AS, the affected individuals have inherited 2 copies of chromosome 15 from their father (paternal uniparental disomy) and no copies of chromosome 15 from their mother. Thus, the individuals with AS resulting from deletion or uniparental disomy are deficient for maternally derived genes from chromosomes 15. Deletions and uniparental disomy occur as de novo events during conception, so the recurrence risk to siblings is very low. Both of these genetic alterations, along with imprinting center defects (accounting for another 2%-5% of AS cases), cause an abnormal methylation pattern in the PWS/AS region of chromosome 15.

Another 10% of patients with AS have a documented mutation in the *UBE3A* gene located in the PW/AS region on chromosome 15. Mutations can either be maternally inherited in an autosomal dominant fashion or de novo. If the mutation is inherited, the risk to all future pregnancies is 50%. If testing of the affected individual's mother confirms she does not carry the mutation, the risk to future pregnancies is low but not zero, as cases of germline mosaicism have been reported. Individuals with a *UBE3A* mutation will display a normal methylation pattern.

No chromosomal or DNA abnormality has been identified in the remainder of clinically diagnosed AS patients (15%-25%). These patients may have genetic alterations that cannot be detected by current testing methods or alterations in as yet unidentified genes.

Initial studies to rule-out AS should include high-resolution cytogenetic analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) to identify chromosome abnormalities that may have phenotypic overlap with AS, and methylation-sensitive, multiple ligation-dependent probe amplification (PWAS / Prader-Willi/Angelman Syndrome, Molecular Analysis) to identify deletions, duplications, and methylation defects. In cases where methylation analysis is negative, sequencing of the *UBE3A* gene may provide additional diagnostic information.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

A small percentage of individuals who are carriers or have a diagnosis of Angelman syndrome caused by a *UBE3A* gene mutation may have a mutation that is not identified by this method (eg, large genomic deletions, promoter mutations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the

diagnosis of Angelman syndrome. For carrier testing, it is important to first document the presence of a *UBE3A* gene mutation in an affected family member.

In some cases, DNA alterations of undetermined significance may be identified.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Methylation analysis (PWAS / Prader-Willi/Angelman Syndrome, Molecular Analysis) is recommended prior to *UBE3A* gene analysis.

Clinical Reference

1. Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May;17(5):405-424

2. Lossie AC, Whitney MM, Amidon D, et al: Distinct phenotypes distinguish the molecular classes of Angelman syndrome. J Med Genet 2001;38:834-845

3. Van Buggenhout G, Fryns JP: Angelman syndrome (AS, MIM 105830). Eur J Hum Genet 2009;17:1367-1373

4. Williams CA, Geaudet AL, Clayton-Smith J, et al: Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet 2006;140A:413-418

Performance

Method Description

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *UBE3A* gene.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly, Varies

Analytic Time

14 days

Maximum Laboratory Time

20 days

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: 3 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81406-UBE3A (ubiquitina protein ligase E3A) (eg, Angelman syndrome), full gene sequence

Fibroblast Culture for Genetic Test

88233-Tissue culture, skin or solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
UBE3Z	UBE3A Gene, Full Gene Analysis	94218-5

Result ID	Test Result Name	Result LOINC Value
54034	Result Summary	50397-9
54035	Result	82939-0
54036	Interpretation	69047-9
54037	Additional Information	48767-8
54038	Specimen	31208-2
54039	Source	31208-2
54040	Released By	18771-6