Test Definition: PWAS

Prader-Willi/Angelman Syndrome, Molecular Analysis, Varies

Overview

Useful For

Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis

Prenatal diagnosis in families at risk for PWS or AS

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CULAF	Amniotic Fluid Culture/Genetic Test	Yes	No
MATCC	Maternal Cell Contamination, B	Yes	No
CULFB	Fibroblast Culture for Genetic Test	Yes	No
_STR1	Comp Analysis using STR (Bill only)	No, (Bill only)	No
_STR2	Add'l comp analysis w/STR (Bill Only)	No, (Bill only)	No

Genetics Test Information

This test is the preferred first-tier test for diagnosis of Angelman syndrome (AS) and Prader-Willi syndrome (PWS). Multiplex ligation probe amplification (MLPA) is used to identify abnormal methylation of the PWS/AS region of chromosome 15.

Testing Algorithm

For prenatal specimens only: If amniotic fluid (nonconfluent cultured cells) is received, amniotic fluid culture/genetic test will be added at an additional charge.

For any prenatal specimen that is received, maternal cell contamination studies will be added.

For more information see Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis.

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

Multiple Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Additional Testing Requirements

Mayo Clinic Laboratories highly recommends that this test be ordered along with a routine chromosomal microarray analysis, CMACB / Chromosomal Microarray, Congenital, Blood, if the diagnosis of Prader-Willi syndrome or Angelman syndrome is not certain and chromosome analysis has not already been done.

All prenatal specimens must be accompanied by a maternal blood specimen. Order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen as **this must be a different order number than the prenatal specimen**.

Specimen Required

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

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: None
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot**.
Specimen Stability Information: Ambient (preferred) 4 days/Refrigerated 4 days/Frozen 4 days
Additional Information:
1. Specimens are preferred to be received within 4 days of collection. Extraction will be attempted for specimens received after 4 days, and DNA yield will be evaluated to determine if testing may proceed.
2. To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

PRENATAL SPECIMENS
Due to its complexity, consultation with the laboratory is required for all prenatal testing; call 800-533-1710 to speak to a genetic counselor.

Specimen Type: Amniotic fluid
Container/Tube: Amniotic fluid container
Specimen Volume: 20 mL
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and/or extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid. An additional 2 to 3 weeks is required to culture amniotic fluid before genetic testing can occur.
3. All prenatal specimens must be accompanied by a maternal blood specimen; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen

Specimen Type: Confluent cultured amniocytes
Container/Tube: T-25 flask
Specimen Volume: 2 Flasks
Collection Instructions: Submit confluent cultured amniocytes from another laboratory.
Specimen Stability Information: Ambient (preferred) <24 hours/Refrigerated <24 hours
Additional Information:
1. Specimens are preferred to be received within 24 hours of collection. Culture and/or extraction will be attempted for specimens received after 24 hours and will be evaluated to determine if testing may proceed.
2. A separate culture charge will be assessed under CULAF / Culture for Genetic Testing, Amniotic Fluid.
3. **All prenatal specimens must be accompanied by a maternal blood specimen**; order MATCC / Maternal Cell Contamination, Molecular Analysis, Varies on the maternal specimen

Specimen Type: Extracted DNA
Container/Tube:
Preferred: Screw Cap Micro Tube, 2mL with skirted conical base
Acceptable: Matrix tube, 1mL
Collection Instructions:
1. The preferred volume is at least 100 mcL at a concentration of 75 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated
Additional Information: DNA must be extracted in a CLIA-certified laboratory or equivalent and must be extracted from a specimen type listed as acceptable for this test (including applicable anticoagulants). Our laboratory has experience with Chemagic, Puregene, Autopure, MagnaPure, and EZ1 extraction platforms and cannot guarantee that all extraction methods are compatible with this test. If testing fails, one repeat will be attempted, and if unsuccessful, the test will be reported as failed and a charge will be applied. If applicable, specific gene regions that were unable to be interrogated due to DNA quality will be noted in the report.

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:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521
3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume
See Specimen Required

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 & Interpretive

Clinical Information
Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are initially poor feeders that improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity. PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS.

Etiology of Prader-Willi syndrome:
-Chromosome 15 deletion (15q11-13): Approximately 60% to 70%
-Maternal uniparental disomy (UPD): 20% to 35%
-Imprinting defect: 1% to 5%
-Chromosome rearrangement: Rare

Paternal deletions of 15q11-13 are more frequently associated with hypopigmentation, characteristic facial features, and skill with jigsaw puzzles, whereas individuals with maternal UPD typically have higher verbal IQ and are more likely to have psychosis and autism spectrum disorder.

Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and intellectual disability, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene *UBE3A*.

Etiology of Angelman syndrome:
-Chromosome 15 deletion (15q11-13): Approximately 70% to 75%
-Paternal UPD: Approximately 5%
-*UBE3A* variant: Approximately 10%
-Imprinting defect: 2% to 5%

-Chromosome rearrangement: Rare
-Unknown: Approximately 10%

The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by paternal UPD or imprinting defects generally show better growth and higher developmental and language abilities.

Both chromosome 15 deletions and UPD most often occur as *de novo* events during conception, and thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements. In these cases, the recurrence risk to siblings is increased.

The recurrence risk associated with imprinting defects is dependent on whether there is an identifiable variant.

UBE3A variants can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited *UBE3A* variant.

Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling.

Initial studies to rule-out PWS or AS should include chromosomal microarray analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where methylation-sensitive MLPA suggests either a deletion or duplication, fluorescence in situ hybridization can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism.

For more information see Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis.

Reference Values

An interpretive report will be provided.

Interpretation

The interpretive report includes an overview of the findings as well as the associated clinical significance.

Cautions

In addition to disease-related probes, the multiple ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Rare variants (ie, 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 the interpretation of results may occur if information given is inaccurate or incomplete.

Methylation status cannot be assessed on chorionic villus specimens.

Rare cases of Prader-Willi syndrome or Angelman syndrome (AS) result from a subtle balanced translocation inherited from one of the parents. These may not be detected by this assay.

A negative molecular test result, especially in the case of a clinical suspicion of AS, does not rule out the diagnosis, because point alterations may not be detected by these methods.

Clinical Reference

1. Buiting K. Prader-Willi syndrome and Angelman syndrome. Am J Med Genet C Semin Med Genet. 2010;154C(3):365-376
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
3. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews [Internet]. University of Washington, Seattle; 1998. Updated November 2, 2023. Accessed November 19, 2024. Available at www.ncbi.nlm.nih.gov/books/NBK1330/
4. Nygren AOH, Ameziane N, Duarte HMB, et al. Methylation-specific MLPA (MS-MLPA): simultaneous detection of CpG methylation and copy number changes of up to 40 sequences. Nucleic Acids Res. 2005;33(14):e128
5. Procter M, Chou LS, Tang W, Jama M, Mao R. Molecular diagnosis of Prader-Willi and Angelman syndromes by methylation-specific melting analysis and methylation-specific multiplex ligation-dependent probe amplification. Clin Chem. 2006;52(7):1276-1283

Performance

Method Description

Methylation-sensitive multiple ligation-dependent probe amplification is utilized to test for the presence of large deletions, duplications and methylation defects in the Prader-Willi/Angelman syndrome critical region.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday, Wednesday

Report Available

10 to 14 days

Specimen Retention Time

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

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Main Campus

Fees & 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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81331-*SNRPN/UBE3A,* (small nuclear ribonucleoprotein polypeptide Nand ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
88235-Tissue culture for amniotic fluid (if appropriate)
88240-Cryopreservation (if appropriate)
81265-Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing or maternal cell contamination of fetal cells (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
PWAS	Prader Willi/Angelman Mol Analysis	35466-2

Result ID	Test Result Name	Result LOINC® Value
52913	Result Summary	50397-9
52914	Result	82939-0
52915	Interpretation	69047-9
52916	Reason for Referral	42349-1
52917	Specimen	31208-2
52918	Source	31208-2
52919	Released By	18771-6