Test Definition: MECPZ

MECP2 Gene, Full Gene Analysis

Overview

Useful For

Diagnosis of Rett syndrome or other *MECP2*-related disorders

Testing Algorithm

See Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm in Special Instruction.

Special Instructions

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Epilepsy: Unexplained Refractory and/or Familial Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) Followed by DNA Sequence Analysis and Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

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.

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.

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

3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

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	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Methyl-CpG-binding protein 2 (MeCP2) is a transcriptional repressor protein encoded by the *MECP2* gene located on the X chromosome. Genetic mutations in *MECP2* alter the expression of targeted genes and can be associated with variable phenotypes in females including classic Rett syndrome, variant or atypical Rett syndrome, mild mental retardation, and asymptomatic carriers. Males with *MECP2* mutations can present with variable phenotypes as well. The variability in males can, in part, be attributed to the type of *MECP2* mutation present; point mutations are typically associated with severe neonatal encephalopathy and gene duplications are associated with *MECP2* duplication syndrome. Full *MECP2* gene analysis via sequencing and large duplication/deletion studies has been useful in identifying germline mutations in individuals with these clinical presentations.

Rett Syndrome:

Rett syndrome is an X-linked, panethnic condition with an incidence of approximately 1 in 8,500 to 1 in 15,000 females. Disease course typically begins after 6 to 18 months of apparently normal development with rapid regression in language and motor skills. A hallmark feature of this condition is repetitive, stereotyped hand movements, sometimes described as hand-wringing. Clinical criteria have been established for diagnosis of classic and atypical or variant Rett syndrome. Greater than 88% of females with a clinical diagnosis of classic Rett syndrome demonstrate a mutation by this test. The detection rate is approximately 43% for females with a clinical diagnosis of atypical or variant Rett syndrome. For individuals in whom there is clinical suspicion for Rett syndrome, but clinical

criteria are not met, the detection rate is lower given the phenotypic overlap with other conditions (eg, Angelman syndrome).

Nonrandom X chromosome inactivation, resulting in phenotypic variability within families, has been reported in females with *MECP2* mutations. Although 99.5% of mutations associated with Rett syndrome are de novo, asymptomatic or very mildly affected carrier mothers of classically affected daughters have been reported. Genetic counseling should be provided with this, and the possibility of germline or somatic mosaicism, in mind.

MECP2 Duplication Syndrome:

Although *MECP2* mutations are reported in males, these males typically do not present with classic Rett syndrome unless an abnormal karyotype (ie, 47,XXY) or somatic mosaicism is also present. More commonly, *MECP2* mutations have been reported in karyotypically normal males presenting with neonatal encephalopathy and mental retardation syndromes. *MECP2* duplication syndrome is an increasingly reported severe mental retardation syndrome characterized by infantile hypotonia, absence of speech, and progressive spasticity. Seizures and recurrent respiratory infections are commonly reported as well. These *MECP2* gene duplications vary in size from 0.3 to 2.3 Mb. Although chromosome analysis can identify some larger duplications, other methods such as multiplex ligation-dependent probe amplification (MLPA) can identify essentially all *MECP2* gene duplications. Males with nongene-duplication type mutations can present with other mental retardation syndromes (ie, Angelman-like syndrome) or neonatal encephalopathy and early death.

To date, all males found to have an *MECP2* duplication are clinically affected and have inherited the duplication from their asymptomatic mothers. Therefore, mothers of sons with *MECP2* duplication syndrome are thought to be obligate carriers whose male offspring have a 50% risk of being affected.

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 a *MECP2*-related disorder may have a mutation that is not identified by this method (eg, promoter mutations, deep intronic alterations). The absence of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of a *MECP2*-related disorder. For carrier testing, it is important to first document the presence of a *MECP2* 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 to us is inaccurate or incomplete.

In addition to disease-related probes, the multiplex ligation-dependent probe 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.

Phenotypic overlap exists between *MECP2*-related conditions and several conditions not associated with *MECP2* mutations. This assay will not detect alterations in other genes or chromosomal rearrangements that could result in a similar phenotype.

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. Moretti P, Zoghbi HY: *MeCP2* dysfunction in Rett syndrome and related disorders. Curr Opin Genet Dev 2006;6(3):276-281.

3. Shahbazian MD, Zoghbi HY: Molecular genetics of Rett syndrome and clinical spectrum of *MECP2* mutations. Curr Opin Genet Dev 2001;14:171-176.

4. Van Esch H, Bauters M, Ignatius J, et al: Duplication of the *MECP2* region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet 2005;77:442-453.

5. Hagberg B, Hanefeld F, Percy A, Skjedal O: An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001 Eur J Paediatr Neurol 2002:6:293-297

6. Laurvick CL, de Klerk N, Bower C, et al: Rett syndrome in Australia: a review of the epidemiology. J Pediatr 2006:148:347-352

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 *MECP2* gene. Additionally, gene dosage analysis (multiplex ligation-dependent probe amplification) is used to test for the presence of large deletions and duplications in this 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

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

81302-*MECP2* (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis

81304-*MECP2* (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
MECPZ	MECP2 Gene, Full Gene Analysis	94229-2

Result ID	Test Result Name	Result LOINC Value
53512	Result Summary	50397-9
53513	Result	82939-0
53514	Interpretation	69047-9
53515	Additional Information	48767-8
53516	Specimen	31208-2
53517	Source	31208-2
53518	Released By	18771-6