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**

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<th>Temperature</th>
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**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**

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


Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society


**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**
Test Definition: MECPZ
MECP2 Gene, Full Gene Analysis

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

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