# MECP2-Related Disorders - Rett Syndrome Testing

*MECP2*-related disorders are a spectrum of disorders with varying severity, including Rett syndrome, *MECP2* duplication syndrome, PPM-X syndrome (the mildest of the *MECP2*-related disorders), and *MECP2* neonatal encephalopathy (the most severe of the *MECP2*-related disorders). In females, *MECP2* disorders include classic and atypical Rett syndrome and intellectual disability. In males, *MECP2* disorders include severe neonatal congenital encephalopathy, intellectual disability, and *MECP2* duplication syndrome.[1] For more information, see the ARUP Consult MECP2-Related Disorders – Classic or Atypical Rett Syndrome topic.

## Testing Strategy

Consultation with a genetic counselor is recommended to determine the optimal *MECP2* genetic testing strategy. The patient's clinical phenotype also guides testing strategy.

- Consider *MECP2* sequencing for:
  - **Females** with
    - A classic or atypical Rett syndrome phenotype
    - Nonspecific intellectual disability
    - Autism
    - Clinically suspected but molecularly unconfirmed Angelman syndrome
  - **Males** with
    - Unexplained neonatal encephalopathy
    - Nonspecific intellectual disability
    - A classic or atypical Rett syndrome phenotype
    - Manic-depressive psychosis, pyramidal signs, Parkinsonian and macroorchidism (PPM-X) syndrome
    - Clinically suspected but molecularly unconfirmed Angelman syndrome
- Consider *MECP2* deletion/duplication analysis for:
  - **Females** when suspicion for classic or atypical Rett syndrome remains despite a negative *MECP2* sequencing result
  - **Males** with suspected *MECP2* duplication syndrome

## Disease Overview

### Rett Syndrome

- Incidence: 1-10,000-15,000 female births
- Clinical phenotype:
  - Highly variable
  - Influenced by sex, age, specific *MECP2* variant, and X-inactivation pattern (females only)
  - See the ARUP Consult MECP2-Related Disorders – Classic or Atypical Rett Syndrome topic for additional information

### *MECP2* Duplication Syndrome

- Incidence:

## Tests to Consider

### Rett Syndrome (MECP2), Sequencing and Deletion/Duplication 0051614

**Method:** Sequencing/Multiplex Ligation-dependent Probe Amplification

- Comprehensive test to confirm a clinical or suspected diagnosis of Rett syndrome or *MECP2*-related disorder
- Determines cause of severe neonatal encephalopathy or intellectual disability in males
- Rules out *MECP2* variant in individuals with clinical features of Angelman syndrome who lack a molecular abnormality involving 15q11.2-13

### Rett Syndrome (MECP2), Full Gene Sequencing 0051378

**Method:** Polymerase Chain Reaction/Sequencing

- Acceptable initial test to confirm a clinical or suspected diagnosis of Rett syndrome or *MECP2*-related disorder
- Determines cause of severe neonatal encephalopathy or intellectual disability in males
- Rules out *MECP2* variant in individuals with clinical features of Angelman syndrome who lack a molecular abnormality involving 15q11.2-13

### Familial Mutation, Targeted Sequencing 2001961

**Method:** Polymerase Chain Reaction/Sequencing

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in a family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED
- Consultation with a genetic counselor is advised

### Deletion/Duplication Analysis by MLPA 3003144

**Method:** Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has

- 1-2% of males with neonatal encephalopathy or moderate to severe intellectual disability
- >200 cases have been reported

- Clinical phenotype
  - Males:
    - Variable intellectual disability in males, including developmental regression in some individuals
    - Hypotonia and feeding problems during infancy
    - Seizures in ~50% of cases
  - Females:
    - Asymptomatic or mild symptoms due to X-inactivation

### *MECP2* Severe Neonatal Encephalopathy

- Incidence:
  - Rare; 20-30 cases reported
- Clinical phenotype:
  - Affects males
  - Brain dysfunction, microcephaly, hypotonia, and seizures
  - Death usually occurs before age 2 due to respiratory failure

### PPM-X Syndrome

- Incidence:
  - Rare; prevalence unknown
- Clinical phenotype
  - Males:
    - Psychotic disorders (commonly bipolar disorder)
    - Movement abnormalities (Parkinsonism)
    - Mild to severe intellectual disability and impaired language development
    - Microcephaly
    - Muscle spasticity
    - May have enlarged testes (macro-orchidism)
  - Females:
    - Mild intellectual disability or learning disability

## Genetics

### Gene

*MECP2*

### Inheritance

- X-linked dominant
- 99.5% of cases are sporadic

### Penetrance

- Nearly 100% in females
- Some females with a *MECP2* variant may be asymptomatic due to skewed X-inactivation
- Disruption of *MECP2* in males is usually lethal

### Variants

>350 known pathogenic variants[2]

- ~95-97% of individuals with classic Rett syndrome have a pathogenic variant in *MECP2*
- ~50%-70% of individuals with atypical Rett syndrome have a pathogenic variant in *MECP2*
- Sequence variants

been identified in a family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

- Majority of *MECP2* sequence variants occur in exon 4
- Deletions/duplications
  - Large deletions most commonly involve exon 3 and/or exon 4 of *MECP2*
  - Males with whole-gene duplications are clinically affected

# Test Interpretation

## Sensitivity/Specificity

- Clinical sensitivity
  - Classic Rett syndrome:
    - Sequencing: ~80%[3,4]
    - Deletions/duplications: ~8-10%[4,5]
  - Atypical Rett syndrome:
    - Sequencing: ~40%[3,4]
    - Deletions/duplications: ~3%[5]
- Analytical sensitivity
  - Sequencing: 99%
  - Deletions/duplications: 90%
- Analytical specificity
  - Sequencing: 99%
  - Deletions/duplications: 98%

## Results

| Result | Findings | Interpretation |
|---|---|---|
| Positive | Pathogenic variant identified | Diagnosis confirmed |
| Negative | No pathogenic variant identified | Possibility of an *MECP2*-related disorder is decreased, but not excluded |
| Uncertain | Variant(s) of uncertain significance identified | Variant(s) may be disease-causing or benign |

## Limitations

- Diagnostic errors may occur due to rare sequence variations or repeat element insertions
- Breakpoints of large deletions/duplications and regulatory region and deep intronic variants are not detected
- Single exon deletion/duplications may not be detected due to probe location

## References


1. Matijevic T, Knezevic J, Slavica M, et al. Rett syndrome: from the gene to the disease. Eur Neurol. 2009;61(1):3-10. PubMed

2. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol. 2010;68(6):944-950. PubMed

3. Fukuda T, Yamashita Y, Nagamitsu S, et al. Methyl-CpG binding protein 2 gene (MECP2) variations in Japanese patients with Rett syndrome: pathological mutations and polymorphisms. Brain Dev. 2005;27(3):211-217. PubMed

4. Li MR, Pan H, Bao XH, et al. MECP2 and CDKL5 gene mutation analysis in Chinese patients with Rett syndrome. J Hum Genet. 2007;52(1):38-47. PubMed

5. Archer HL, Whatley SD, Evans JC, et al. Gross rearrangements of the MECP2 gene are found in both classical and atypical Rett syndrome patients. J Med Genet. 2006;43(5):451-456. PubMed


# Additional Resources

National Institutes of Health, U.S. National Library of Medicine. MECP2 gene. [Last reviewed: Mar 2017; Accessed: Jul 2020]

Percy AK, Lane JB, Childers J, et al. Rett syndrome: North American database. J Child Neurol. 2007;22(12):1338-1341. PubMed

## Related Information

MECP2-Related Disorders - Classic or Atypical Rett Syndrome
Laboratory Testing for Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder
Testing for Genetic Syndromes Related to Developmental Delay (DD), Intellectual Disability (ID), and Autism Spectrum Disorder (ASD)

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com
Content Review September 2020 | Last Update February 2021