

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

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

- 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 variants²

- ~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
 - 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 <i>MECP2</i> -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 \(ASD\)](#)

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Content Review September 2020 | Last Update November 2020