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. (Matijevic, 2009) For more information, see the MECP2-Related Disorders – Classic or Atypical Rett Syndrome Consult topic. ¹

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:
  o Highly variable
  o Influenced by sex, age, specific *MECP2* variant, and X-inactivation pattern (females only)
  o See the MECP2-Related Disorders – Classic or Atypical Rett Syndrome Consult topic for additional information

**MECP2 Duplication Syndrome**

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

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

**MECP2 Severe Neonatal Encephalopathy**

• Incidence:
  o Rare; 20-30 cases reported

• Clinical phenotype:
  o Affects males
    o Brain dysfunction, microcephaly, hypotonia, and seizures
    o Death usually occurs before age 2 due to respiratory failure

**PPM-X Syndrome**

• Incidence:
  o Rare; prevalence unknown

• Clinical phenotype
  o 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)
  o 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

- ~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**

<table>
<thead>
<tr>
<th>Result</th>
<th>Findings</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Pathogenic variant identified</td>
<td>Diagnosis confirmed</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variant identified</td>
<td>Possibility of an MECP2-related disorder is decreased, but not excluded</td>
</tr>
</tbody>
</table>
Result | Findings | Interpretation
--- | --- | ---
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


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 | arulab.com | arupconsult.com

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