

## Rett Syndrome - MECP2 Disorders

### Clinical Background

*MECP2* disorders in females include classic and atypical Rett syndrome, and learning disabilities. In males, *MECP2* disorders include congenital encephalopathy, atypical Rett syndrome, mental retardation, and *MECP2* duplication syndrome.

#### Epidemiology

- Prevalence of Rett syndrome – 1/10,000
- Age – early childhood
- Sex – M<F

#### Inheritance

- X-linked dominant with almost 100% penetrance
- Most *MECP2* sequence changes or deletions are *de novo*; however, *MECP2* duplications are maternally inherited
- The majority (~80%) of *MECP2* mutations are sequence variants, up to 15% are deletions, gene duplications are rare and detectable by routine cytogenetic analysis in approximately 5% of cases
- *MECP2* deletions or nonsense mutations are generally associated with a more severe phenotype than missense mutations
- *MECP2* mutations are variably expressed based on sex and pattern of X-chromosome activation (in females)

#### Pathophysiology

- Probable abnormal development of the cortex in infancy
- Dysregulation of the autonomic system and associated brainstem dysregulation

#### Clinical Presentation

- Clinical severity is influenced by the patient's sex, the specific *MECP2* mutation, and pattern of X inactivation (in females).
- Classic Rett
  - Typically seen in affected females; males with a 47,XXY karyotype and an *MECP2* mutation, or males with somatic *MECP2* mutations, may also present with classic Rett syndrome
  - Apparently normal prenatal and perinatal history
  - Normal growth and development until 6-18 months of age followed by rapid neurodevelopmental regression
  - Normal head circumference at birth with postnatal head growth deceleration
  - Purposeful hand movements replaced with repetitive stereotyped hand movements
  - Loss of acquired speech
  - Non-ambulatory or gait ataxia
  - Social withdrawal or autistic features
  - Associated findings include: seizures (occur in up to 90%), abnormal EEG, breathing irregularities, sleep disturbances, bruxism and scoliosis
- Atypical Rett
  - Possible phenotype in females or males
  - Rett-like features that do not completely meet clinical criteria; may be either milder or more severe than classic Rett syndrome

- Congenital encephalopathy
  - Possible phenotype in males
  - Often associated with microcephaly, abnormal tone, involuntary movements, severe seizures, breathing abnormalities and death before the age of two
- Mild to severe mental retardation (developmental delay)
  - Possible phenotype in males or females; females with mild phenotypes may have highly skewed X-chromosome inactivation
- *MECP2* duplication syndrome
  - Severity among affected males is usually consistent within families; however, interfamilial variability may occur
    - Infantile hypotonia
    - Severe mental retardation
    - Absence of speech
    - Progressive spasticity
    - Recurrent respiratory infections (75%)
    - Seizures (50%)
  - Female carriers are unaffected due to skewed X inactivation (in cases reported to date)

#### Treatment

- Mainly supportive
- Seizure control may require drug therapy
- Pharmacological therapies to reduce agitation, hyperventilation or sleep dysfunction may be used
- Restraints may be considered to prevent self injurious behavior and reduce agitation
- Assessment of feeding and digestive issues (constipation and reflux are common)
- Bracing or surgical intervention for scoliosis
- Avoid use of drugs associated with prolongation of QT interval (prokinetic agents, antipsychotics, antiarrhythmics, anesthetic agents, etc.)

## Diagnosis

- Indications for testing – clinical diagnosis suggested by presence of clinical criteria
- Laboratory testing
  - To confirm a clinical diagnosis of Rett syndrome or an *MECP2*-related disorder
  - To rule out an *MECP2* mutation in families with X-linked mental retardation
    - *MECP2* sequencing – 80% clinical sensitivity
    - *MECP2* duplication/deletion analysis – clinical sensitivity up to 15%
    - CGH array – detection of large deletions or duplications only
  - Targeted testing should be offered to parents who have a child with an *MECP2* mutation to help define recurrence risk

#### Differential Diagnosis

- Angelman syndrome
- Autism
- Cerebral palsy
- Inborn errors of metabolism (in males with congenital encephalopathy)
- Mental retardation

## Screening

- Prenatal diagnosis of subsequent pregnancies of a couple who have a child with an identified *MECP2* mutation should be offered (germline mosaicism cannot be excluded)

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
Rett Syndrome ( <i>MECP2</i> ), Full Gene Analysis <b>0051614</b> Method: Full Gene Sequencing/Multiplex Ligation Probe Amplification	Diagnose atypical or classic Rett syndrome  Components include <i>MECP2</i> sequencing and duplication/deletion analysis by MLPA. Clinical sensitivity up to 95%  Clinical sensitivity up to 95%	Breakpoints of large deletions/duplications will not be determined; deep intronic mutations will not be detected; rare diagnostic errors can occur due to primer or probe site mutations	Counseling and informed consent are recommended for genetic testing
Rett Syndrome ( <i>MECP2</i> ), Deletion and Duplication <b>0051618</b> Method: Multiplex Ligation Probe Amplification	Order for females with classic Rett syndrome negative by <i>MECP2</i> sequencing or males with a phenotype suggestive of an <i>MECP2</i> copy number variation  Clinical sensitivity up to 15%	Deletion/duplication breakpoints will not be determined; deep intronic mutations, single base pair substitutions and small deletions/duplications will not be detected; rare diagnostic errors can occur due to probe site mutations	Counseling and informed consent are recommended for genetic testing
Rett Syndrome ( <i>MECP2</i> ), Full Gene Sequencing <b>0051378</b> Method: Polymerase Chain Reaction/Sequencing	Diagnose atypical or classic Rett syndrome  Clinical sensitivity up to 80%	Deep intronic mutations and large deletions/duplications will not be identified; rare diagnostic errors can occur due to primer site mutations	Counseling and informed consent are recommended for genetic testing
Deamidated Gliadin Peptide (DGP) Antibodies, IgA & IgG <b>0051358</b> Method: Enzyme-Linked Immunosorbent Assay	Targeted sequencing for a previously identified familial <i>MECP2</i> mutation	Rare diagnostic errors can occur due to primer site mutations	Counseling and informed consent are recommended for genetic testing

### General References

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