

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.

Test Name and Number	Recommended Use	Limitations	Follow Up
Rett Syndrome (<i>MECP2</i>), Full Gene Analysis 0051614 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 0051618 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 0051378 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 0051358 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

Glaze DG. Neurophysiology of Rett syndrome. *J Child Neurol.* 2005; 20 (9) :740-746.

Huppke P, Gartner J. Molecular diagnosis of Rett syndrome. *J Child Neurol.* 2005; 20 (9) :732-736.

Lotan M, Ben-Zeev B. Rett syndrome. A review with emphasis on clinical characteristics and intervention. *ScientificWorldJournal.* 2006; 6 :1517-1541.

MECP2-Related Disorders. GeneTests. University of Washington, Seattle [Last Updated: 2 Apr 2009; Accessed: 20 Apr 2009]

Moretti P, Zoghbi HY. MeCP2 dysfunction in Rett syndrome and related disorders. *Curr Opin Genet Dev.* 2006; 16 (3) :276-281.

Nomura Y, Segawa M. Natural history of Rett syndrome. *J Child Neurol.* 2005; 20 (9) :764-768.

Percy AK. Rett syndrome: recent research progress. *J Child Neurol.* 2008; 23 (5) :543-549.

Segawa M, Nomura Y. Rett syndrome. *Curr Opin Neurol.* 2005; 18 (2) :97-104.

Weaving LS, Ellaway CJ, Gecz J, Christodoulou J. Rett syndrome: clinical review and genetic update. *J Med Genet.* 2005; 42 (1) :1-7.

Williamson SL, Christodoulou J. Rett syndrome: new clinical and molecular insights. *Eur J Hum Genet.* 2006; 14 (8) :896-903.

Reviewed by

Bayrak-Toydemir, Pinar, MD, PhD. Associate Medical Director, Molecular Genetics at ARUP Laboratories; Assistant Professor of Pathology (Clinical), University of Utah

Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Developmental Delay (DD) Testing Algorithm

Related Content

Developmental Delay (DD) or Mental Retardation (MR) Testing - Neurocognitive Impairments

Comprehensive Review: March 2009

Last Update: March 2009