

# Rett Syndrome (*MECP2*) Sequencing and Deletion/ Duplication

*TO DIAGNOSE OR DETERMINE CARRIER STATUS OF  
INDIVIDUALS WITH RETT SYNDROME OR METHYL-CpG-  
BINDING PROTEIN 2 (MECP2) GENE-RELATED DISORDERS*

## Disease Overview

- Classic Rett syndrome is a progressive neurodevelopmental disorder characterized by rapid developmental regression, deceleration of head growth, and loss of speech and acquired motor skills after six to 18 months of age. Purposeful use of the hands is replaced by repetitive stereotyped hand movements.
- Additional findings may include: seizures, autistic features, episodic apnea, gait ataxia, bruxism, and growth retardation.
- *MECP2* is the only gene known to be associated with classic Rett syndrome.
- Rett syndrome is an isolated occurrence in families 99.5 percent of the time.
- *MECP2* mutations in females most often result in classic Rett syndrome, but may cause atypical Rett syndrome or mild learning disabilities due to skewed X chromosome inactivation.
- *MECP2* mutations in males can result in variable clinical presentations including, Rett-like syndrome, severe congenital encephalopathy, or mild to severe mental retardation. Management of symptoms often involves a multidisciplinary approach and is aimed at optimizing the patient's abilities.

## Epidemiology

- Prevalence of Rett syndrome is approximately one in 10,000.
- Classic Rett syndrome is more common in females than males.

## Genetics

- X-linked dominant inheritance with nearly 100 percent penetrance.
- Most *MECP2* mutations are de novo.
- Approximately 80 percent of deleterious *MECP2* mutations are sequence changes, while large deletions of *MECP2* may comprise up to 15 percent of causative mutations. Deletions are more common in individuals with classic vs. atypical Rett syndrome.
- As germline mosaicism cannot be excluded by parental *MECP2* testing, prenatal diagnosis for subsequent pregnancies should be offered to couples with a child identified as having an *MECP2* mutation.

## Indications for Ordering

- To confirm a clinical diagnosis of Rett syndrome or a *MECP2*-related disorder.
- To determine the cause of severe neonatal encephalopathy or mental retardation in males.
- To rule out an *MECP2* mutation in families with X-linked mental retardation.
- To rule out an *MECP2* mutation in individuals with clinical features of Angelman syndrome where molecular confirmation has been unsuccessful.

## Interpretation

- One *MECP2* mutation is causal for classic Rett syndrome in females, but a milder phenotype may result.
- One *MECP2* mutation is associated with a variable phenotype in males.
- *MECP2* variants of unknown clinical significance may be detected.

## Limitations

- Rare diagnostic errors can occur due to primer or probe site mutations.
- Regulatory region mutations and deep intronic mutations will not be detected.
- The breakpoints of large deletions/duplications will not be determined.

## Methodology

- Bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA) of all *MECP2* coding regions and exon/intron borders.
- Combined clinical sensitivity of *MECP2* gene sequencing and deletion/duplication testing is up to 95 percent. Analytic sensitivity and specificity of sequencing are 99 percent. Analytic sensitivity and specificity of MLPA are 90 and 98 percent, respectively.

### Related Tests

- Rett Syndrome (*MECP2*), Full Gene Sequencing (0051378)
- Rett Syndrome (*MECP2*), Deletion and Duplication (0051618)
- *Rickettsia typhi* (Typhus Fever) Antibody, IgM by IFA (0050383). Custom PCR and Sequencing (targeted sequencing for a *MECP2* sequence change previously identified in a family member)

### References

1. Bienvenu T, Chelly J. Molecular genetics of Rett syndrome: when DNA methylation goes unrecognized. *Nat Rev Genet* 2006; 7:415–26.
2. Ravn K, et al. Large genomic rearrangements in *MECP2*. *Hum Mutat* 2005; 25(3):324.
3. Kleefstra T, et al. *MECP2* analysis in mentally retarded patients: implications for routine DNA diagnostics. *Eur J Hum Genet* 2004; 12:24–8.

## Test Information

### 0051614 Rett Syndrome (*MECP2*), Full Gene Analysis

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).