

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

DIAGNOSTIC OR CARRIER TESTING FOR RETT SYNDROME OR METHYL-CPG-BINDING PROTEIN 2 (MECP2) GENE-RELATED DISORDERS

Disease Overview

- Classic Rett syndrome
 - 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 6 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.
- *MECP2* duplication syndrome
 - *MECP2* duplication syndrome is a severe neurodevelopmental condition.
 - Males with duplications of *MECP2* have a variable clinical presentation, including: infantile hypotonia, developmental disabilities, progressive spasticity, recurrent infections, and seizures.
 - Females who carry a *MECP2* duplication are typically asymptomatic due to skewed X- chromosome inactivation; however, clinical presentations may be variable.

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.
- Duplications of *MECP2* may occur in 1–2 percent of males with severe encephalopathy or moderate to severe intellectual disability.
- 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 pathogenic *MECP2* mutation is often causal for classic Rett syndrome in females, but milder phenotypes may result.
- One pathogenic *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 of the *MECP2* coding region and exon/intron boundaries; multiplex ligation-dependent probe amplification (MLPA) to detect large deletions/duplications in the *MECP2* coding-region.
- 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)
- Familial Mutation, Targeted Sequencing (2001961)

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.
4. Lugtenberg D, Kleefstra T, Oudakker AR, et al. Structural variation in Xq28: *MECP2* duplications in 1% of patients with unexplained XLMR and in 2% of male patients with severe encephalopathy. *Eur J Hum Genet* 2009;17:444–53.

Test Information

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

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.