



***MECP2* DNA Sequence Analysis for Rett Syndrome Is Now Available**

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Rett syndrome (RTT; MIM 312750) is an X-linked progressive disorder that almost exclusively affects females with an incidence of 1 in 10,000–20,000. It is characterized by deceleration of head growth, loss of acquired skills, and mental retardation. Diagnostic criteria and disease stages for RTT were established (Hagberg et al., 1985). Patients with classic RTT appear to develop normally until 6–18 months of age, then gradually lose social and communication skills and purposeful hand use. During this regression period, RTT patients develop a complex syndrome that includes acquired microcephaly, seizures, irregular breathing patterns, scoliosis, and autonomic dysfunction. Most of the ambulant patients have a wide-based, apraxic gait. After the initial period of regression, the condition stabilizes and patients usually survive into adulthood.

Amir et al. (1999) identified mutations in the X-linked *MECP2* gene, which encodes the protein MeCP2, as the main cause of RTT. *MECP2* mutations have also been found in females with atypical RTT and in males with severe neonatal encephalopathy, as well as in patients with clinical features of Angelman syndrome, Klinefelter syndrome, autism, mental retardation, resting tremors, or progressive spasticity. Currently, the most accurate method to confirm the clinical diagnosis of RTT uses PCR followed by DNA sequence analyses of exons 1, 2, 3, and 4 of the *MECP2* gene. The test has close to 100% specificity and is approximately 85% sensitive. This method may not detect large deletions or rearrangements in *MECP2*, or mutations in genes other than *MECP2*. A broad spectrum of *MECP2* mutations has been observed within the coding region of the gene, including missense and nonsense mutations, deletions, and insertions. However, eight common point mutations are found in approximately 70% of the cases. In general, RTT is caused by the loss of MeCP2 function regardless of the precise mutation involved.

MeCP2 is a ubiquitously expressed protein with two well-defined domains: an 85-amino acid methyl-cytosine binding domain (MBD) and a 102-amino acid transcriptional repression domain (TRD). Although the protein is expressed ubiquitously, the loss of function of MeCP2 results in a phenotype associated with the central nervous system.

References

- Amir, RE et al. (1999) Rett syndrome is caused by mutations in X-linked *MECP2*, encoding methyl-CpG-binding protein 2. *Nat Genet* 23, 185-188.
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- Hagberg, B (1985) Rett's syndrome: prevalence and impact on progressive severe mental retardation in girls. *Acta Paediatr Scand* 74, 405–408.
- Shahbazian, MD & Zoghbi, HY (2002) Rett syndrome and MeCP2: linking epigenetics and neuronal function. *Am J Hum Genet* 71, 1259-1272.

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Quick Facts

- ▶ **Rett syndrome is a progressive neurological disorder affecting mostly females.**
- ▶ **About 85% of Rett syndrome cases are caused by mutations in the *MECP2* gene.**
- ▶ ***MECP2* mutations have also been found in females with atypical Rett syndrome.**
- ▶ **Males with severe neonatal encephalopathy and patients with clinical features of Angelman syndrome, Klinefelter syndrome, autism, mental retardation, resting tremors, or progressive spasticity may also have mutations in *MECP2*.**
- ▶ **PCR and DNA sequence analyses are used to detect point mutations or small rearrangements in the *MECP2* gene.**

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Test Information

DESCRIPTION **RET T SYNDROME (MECP2 DNA ANALYSIS)**

METHOD PCR, Sequencing

ORDER CODE RRETT

CPT CODE 83891, 83898 × 4, 83904 × 11, 83912

SAMPLE 5 mL EDTA, ACD or sodium citrate whole blood (lavender, yellow, or blue-top tube). Submit original unopened tube only. Store and transport at room temperature or refrigerated. Include patient's family history and clinical indication for testing.

This test must be ordered on a paper requisition that accompanies the sample. It is not orderable on the PAML computer system.

COMMENTS *Minimum amount:* 3 mL

Unacceptable conditions: plasma, serum, heparinized whole blood, frozen whole blood, severely hemolyzed samples, samples in leaking containers or over 5 days old, samples not received in the original collection tubes.

Stability: 72 hours at room temperature, 5 days refrigerated, unacceptable frozen.

SCHEDULE Weekly

TURNAROUND 2-3 weeks

RANGES Result
Interpretation
Comment