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MeCP2 analysis

Clinical Features:

Rett syndrome is a progressive neurodevelopmental disorder, primarily affecting females. Rett syndrome is characterized by acquired microcephaly, loss of purposeful hand movements, and autistic behaviors, following a period of normal growth and development. Additional features include scoliosis, epilepsy, poor growth, and irregular breathing [1]. There is broad clinical variability in the severity of Rett syndrome, including a milder variant of Rett syndrome [2].

Inheritance:

Rett syndrome is an X linked condition that occurs in 1 in 10,000 to 1 in 15,000 live births. The majority (99.5%) of cases are *de novo* [2]. Recurrence risk for unaffected parents and no family history is less than 1%. There have been reports of unaffected or mildly affected carrier females due to skewed X inactivation. Recurrence risk for a carrier female is 50%.

Molecular Genetics:

Rett syndrome is caused by mutations in the *MeCP2* (methyl-CpG-binding protein) gene located at Xq28 [3]. *MeCP2* has 4 exons and two functional domains that are involved in gene silencing and transcriptional repression. *MeCP2* expression is essential for synapse maturation and maintenance. Several different mutations have been identified in the *MeCP2* gene including nonsense mutations, missense mutations, and deletions. Sequence mutations are present in 80% of girls with classic Rett syndrome and 20% of girls with a variant diagnosis. *MeCP2* deletions are found in approximately 16% of girls with classic Rett syndrome and no previously identified sequence mutation [2].

Other conditions caused by alterations in *MeCP2*:

- Females with atypical Rett syndrome (preserved speech variant or congenital onset)
- Males with moderate to severe, non-specific mental retardation and encephalopathy
- Males with features similar to classic Rett syndrome
- Families with X-linked mental retardation
 - ~2% of males with X-linked mental retardation have mutations in *MeCP2* [4]
 - Four male patients with severe mental retardation and progressive neurological symptoms were recently reported to have microduplications in *MeCP2*. Three of these patients were from large families consistent with X-linked mental retardation. Of the 13 affected males, features reported in more than half of them included: severe mental retardation, spasticity, facial hypotonia, and absent speech. Female carriers in this study were asymptomatic and demonstrated skewed X-inactivation [5].
- Children with Angelman syndrome-like phenotype but normal methylation and *UBE3A* studies
 - Approximately 10% have a *MeCP2* mutation [6].

Additional Resources:

International Rett Syndrome Association (IRSA)
Phone: 800-818-7388; 301-856-3334
Email: irsa@rettsyndrome.org
www.rettsyndrome.org

Test methods:

We offer full gene sequencing for all four coding exons and the intron/exon boundaries of *MeCP2*. We also offer deletion/duplication analysis of the *MeCP2* gene by MLPA to identify deletions/duplications of one or more exons. Deletion/duplication analysis will identify deletions in females as well as duplications in males or females. The sensitivity of our deletion/duplication assay may be reduced when DNA is extracted by an outside laboratory. For best results, please provide a fresh blood sample for this testing.

Mutation analysis (sequencing and deletion/duplication analysis)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$1400
CPT codes: 83891, 83898 x2, 83904 x4, 83900, 83901 x2, 83912
Turn-around time: 4 – 6 weeks

Sequencing analysis

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$925
CPT codes: 83898 x 3, 83904 x 4
Turn-around time: 4 – 6 weeks

Deletion/duplication analysis for females

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$350
CPT codes: 83891, 83900, 83912
Turn-around time: 4 weeks

Duplication analysis for males

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$350
CPT codes: 83891, 83900, 83912
Turn-around time: 4 weeks

Targeted analysis for a known sequence change in additional family members

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$390
CPT codes: 83891, 83898 x 2, 83894, 83912
Turn-around time: 3-4 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amniocentesis or CVS
Cost: \$550-590
CPT codes: please contact us for specific CPT codes
Turn-around time: 1 – 2 weeks

Laboratory Faculty and Staff:

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References:

1. Hagberg B, *et al.*, (1985) Rett syndrome: criteria for inclusion and exclusion. *Brain Dev* 7(3): 372-3.
2. Zoghbi HY, (2004) Rett syndrome. www.genetests.org
3. Amir RE, *et al.*, (1999) Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG binding protein 2. *Nat Genet* 23: 185-8.
4. Couvert P, *et al.*, (2001) MECP2 is highly mutated in X-linked mental retardation. *Hum Mol Genet* 10(9): 941-6.
5. Von Esch H, *et al.*, (2005) Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet* 77: 442-5.
6. Watson P, *et al.*, (2001) Angelman syndrome phenotype with mutations in MECP2, a gene encoding a methyl CpG binding protein. *J Med Genet* 38(4): 224-8.

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