The University of Chicago Genetic Services Laboratories

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CLIA #: 14D0917593 CAP #: 18827-49

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 (5).

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 or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced

translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

MECP2 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$900
CPT codes:	81302
Turn-around time:	4 weeks

MECP2 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81304
Turn-around time:	4 weeks

Testing for a known mutation in additional family members by sequence analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	81403
Turn-around time:	3-4 weeks

Prenatal testing for a known mutation by sequence analysis

Sample specifications:	2 T25 flasks of cultured cells from amniocentesis or CVS or 10 mL of amniotic fluid
Cost:	$540
CPT codes:	81403
Turn-around time:	1-2 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Hagberg B, Goutières F, Hanefeld F et al. Rett syndrome: criteria for inclusion and exclusion. Brain Dev 1985: 7: 372-373.
2. Amir RE, Van den Veyver IB, Wan M et al. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999: 23: 185-188.
3. Couvert P, Bienvenu T, Aquaviva C et al. MECP2 is highly mutated in X-linked mental retardation. Hum Mol Genet 2001: 10: 941-946.
4. Van Esch H, Bauters M, Ignatius J et al. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet 2005: 77: 442-453.
5. Watson P, Black G, Ramsden S et al. Angelman syndrome phenotype associated with mutations in MECP2, a gene encoding a methyl CpG binding protein. J Med Genet 2001: 38: 224-228.

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