



The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
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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 real time-quantitative PCR to detect intragenic deletions or duplications. Please note that **we cannot accept DNA extracted in other labs 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 (real time-quantitative PCR) for females

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$550
CPT codes: 83891, 83900, 83901 x 2, 83912
Turn-around time: 4 weeks

Duplication analysis (real time-quantitative PCR) for males

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$450
CPT codes: 83891, 83898 x 4, 83912
Turn-around time: 4 weeks

Testing for a known mutation in additional family members

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: \$390-\$450
CPT codes: please contact us for specific CPT codes
Turn-around time: 2 – 3 weeks

Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amniocentesis or CVS
Cost: \$590-\$650
CPT codes: please contact us for specific CPT codes
Turn-around time: 1 – 2 weeks

Results:

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

Soma Das, Ph.D.
Director, Molecular Genetics Laboratory
ABMG Certified Molecular Geneticist

Stuart Schwartz, Ph.D.
Director, Cytogenetics Laboratory
ABMG Certified Cytogeneticist

Melissa Dempsey, M.S.
ABGC Certified Genetic Counselor

Darrel J. Waggoner, M.D., and William B. Dobyns, M.D.
Clinical Advisors/ABMG Certified Clinical Geneticists

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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