

The University of Chicago Genetic Services Laboratories



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Infantile Spasms/Atypical Rett Syndrome Panel

Clinical Features:

Infantile spasms involve momentary flexion of the neck, trunk, or extremities, onset within the first year of life and subsiding during late infancy. Affected children may develop other seizures and have severe developmental delays. West syndrome is the triad of infantile spasms, hypsarrhythmia, and severe mental retardation.

Rett syndrome is a progressive neurodevelopmental disorder, primarily affecting females. The Hanefeld variant describes females with atypical Rett syndrome and infantile spasms or early-onset epileptic seizures.

There is much overlap between the clinical features and etiology of infantile spasms, Rett syndrome and atypical Rett syndrome.

- Up to 10% of patients with a clinical diagnosis of West syndrome/cryptogenic infantile spasms and X-linked mental retardation may have mutations in the *ARX* gene [1,2].
- *MeCP2* mutations are present in 70-90% of females with classic Rett syndrome and approximately 20% of females with atypical Rett syndrome [3].
- Partial deletions of *MeCP2* are found in approximately 16% of girls with classic or atypical Rett syndrome [3].
- The most common feature found in patients reported to date with *CDKL5/STK9* mutations is the early onset of seizures. 13/14 patients studied had seizures before 3 months of age [4].

Inheritance:

CDKL5, *ARX*, and *MeCP2* are X-linked. *CDKL5* and *MeCP2* mutations appear to be more common in females than in males. The majority of cases are *de novo*. There have been reports of unaffected or mildly affected *MeCP2* carrier females due to skewed X inactivation, and there has been one family reported with multiple affected siblings with a *CDKL5* mutation [5]. *ARX* mutations are more commonly associated with infantile spasms in males and carrier females can be asymptomatic [1,2]. Recurrence risk for a carrier female is 50%.

Molecular Genetics:

ARX (Aristaless Related Homeobox; OMIM #300382) encodes for a transcription factor expressed primarily in fetal and adult brain and skeletal muscle and is important for the maintenance of specific neuronal subtypes in the cerebral cortex and axonal guidance in the floor plate. *MeCP2* (methyl-CpG-binding protein; OMIM #300005) has two functional domains that are involved in gene silencing and transcriptional repression, and *MeCP2* expression is essential for synapse maturation and maintenance. *CDKL5* (cyclin-dependent kinase-like 5; OMIM #300203) contains a serine/threonine kinase domain and has been implicated in *MeCP2* modification *in vitro* suggesting that *MECP2* and *CDKL5* belong to the same molecular pathway [6]. Both *ARX* and *CDKL5* are located at Xp22, and *MeCP2* is located at Xq28.

Additional Resources:

West Syndrome Support Group
www.wssg.org.uk

International Rett Syndrome Association
Phone: 1-800-818-RETT
Email: admin@rettsyndrome.org
www.rettsyndrome.org

Test methods:

We offer full gene sequencing for all coding exons and the intron/exon boundaries of *MECP2*, *ARX*, and *CDKL5*. We also offer MLPA and real time-quantitative PCR to detect intragenic deletions within *MECP2*. These tests are offered together as a panel or separately.

Infantile spasms/atypical Rett syndrome panel
(MeCP2 sequencing and deletion analysis, ARX and CDKL5 sequencing)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$3950
CPT codes: 83891, 83898 x 8, 83904 x 16, 83900, 83901 x 2, 83912
Turn-around time: 6 – 8 weeks

MeCP2 sequencing

Sample specifications: 3 to10 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

MeCP2 deletion analysis (real time-quantitative PCR)

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$550
CPT codes: 83891, 83900, 83901 x 2, 83912
Turn-around time: 4 weeks

ARX sequencing

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$1000
CPT codes: 83891, 83898 x2, 83904 x4, 83912
Turn-around time: 4 - 6 weeks

CDKL5 sequencing

Sample specifications: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$2025
CPT codes: 83891, 83898 x 4, 83904 x 9, 83912
Turn-around time: 4 – 6 weeks

Testing for a known mutation/deletion in additional family members

Sample specifications: 3 to10 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: 3 to10 cc of blood in a purple top (EDTA) tube
Cost: \$590-\$650
CPT codes: please contact us for specific CPT codes
Turn-around time: 1 – 2 weeks

Results

Results, along with an interpretive report, are faxed and mailed to the referring physician as soon as it they are completed. Additional reports are available as requested. One report will be issued for all of the tests in the infantile spasms panel. All abnormal results are reported by telephone.

Laboratory Faculty and Staff:

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References:

1. Stromme et al., Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy (2002) *Nature Genet.* 30:441-445.
2. Bienvenu T, et al. ARX, a novel Prd-class-homeobox gene highly expressed in the telencephalon, is mutated in X-linked mental retardation (2002) *Hum Mol Genet* 11: 981-91.
3. Zoghbi HY, (2004) Rett syndrome. www.genetests.org
4. Evans, et al., Early onset seizures and Rett-like features associated with mutations in CDKL5. (2005) *Eur J Hum Genet*, ePub July 13.
5. Weaving LS, et al. Mutations of *CDKL5* cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. (2004) *Am J Hum Genet* 75: 1079-93.
6. Mari F, et al. *CDKL5* belongs to the same molecular pathway of *MeCP2* and it is responsible for the early-onset seizure variant of Rett syndrome. (2005) *Hum Molec Genet* 14(14): 1935-46.

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