The University of Chicago Genetic Services Laboratories

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CDKL5 Gene Sequencing

Clinical Features:

CDKL5 mutations have been demonstrated in a broad spectrum of phenotypes (1-5), including:

- X-linked infantile spasms (ISSX) or West syndrome—triad of infantile spasms, hypsarrhythmia, and severe mental retardation
- Infantile epileptic encephalopathy
- Otohara syndrome
- Atypical Rett syndrome with infantile spasms or the Hanefeld variant
- Mild mental retardation and autism
- Angelman syndrome-like phenotype

This phenotype overlaps most with that of ISSX and Rett syndrome, caused by mutations in *ARX* and *MECP2*. Thus, many of these patients are also candidates for *ARX* and/or *MECP2* analysis. The most common feature found in patients reported to date with *CDKL5* mutations is the early onset of seizures. 13/14 patients studied had seizures before 3 months of age (3).

Inheritance:

CDKL5 mutations are X-linked and appear to be less common in males than females, though few male patients have been studied. Whether these mutations are normally lethal in males remains unclear. One report of affected identical twin sisters and an affected brother with unaffected parents indicates the possibility of gonadal mosaicism [2]. All other reported mutations are *de novo* (3)

Molecular Genetics:

The *CDKL5* gene codes for the cyclin-dependent kinase-like 5 or serine threonine kinase 9 (STK9) protein (OMIM #300203) and is located at Xp22 (1-5). This protein contains a serine/threonine kinase domain and has been implicated in *MeCP2* modification *in vitro*, but overall remains rather uncharacterized. These findings, along with an overlap in phenotypes and expression patterns, suggest that *MECP2* and *CDKL5* belong to the same molecular pathway (6). *CDKL5* has 20 coding exons.

Mei et al (2009) detected 4 *CDKL5* mutations and 4 *CDKL5* deletions in 49 total girls with early onset intractable epilepsy and developmental impairment (7). Several different mutations have been identified in the *CDKL5* gene including missense, frameshift, and splicing mutations, along with deletions.

Additional Resources:

International Foundation for CDKL5 Research
Phone: 330-612-2751 or 630-926-1189
Email: admin@rettsyndrome.org
www.cdkl5.com

International Rett Syndrome Association
Phone: 1-800-818-RETT
Fax: 301-856-3336
Email: admin@rettsyndrome.org
www.rettsyndrome.org

Test methods:

We offer analysis of all 20 coding exons and intron/exon boundaries of *CDKL5* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *CDKL5* 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. For best results, please provide a fresh blood sample for this testing.

CDKL5 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1700
CPT codes:	81406
Turn-around time:	4 weeks

CDKL5 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
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 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 week

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. Tao J, Van Esch H, Hagedorn-Greiwe M et al. Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation. Am J Hum Genet 2004: 75: 1149-1154.
2. Weaving LS, Christodoulou J, Williamson SL et al. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet 2004: 75: 1079-1093.
3. Evans JC, Archer HL, Colley JP et al. Early onset seizures and Rett-like features associated with mutations in CDKL5. Eur J Hum Genet 2005: 13: 1113-1120.
4. Scala E, Ariani F, Mari F et al. CDKL5/STK9 is mutated in Rett syndrome variant with infantile spasms. J Med Genet 2005: 42: 103-107.
5. Kalscheuer VM, Tao J, Donnelly A et al. Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation. Am J Hum Genet 2003: 72: 1401-1411.
6. Mari F, Azimonti S, Bertani I et al. CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. Hum Mol Genet 2005: 14: 1935-1946.
7. Mei D, Marini C, Novara F et al. Xp22.3 genomic deletions involving the CDKL5 gene in girls with early onset epileptic encephalopathy. Epilepsia 2010: 51: 647-654.

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