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 to 10 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 to 10 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 to 10 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  
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:**