

CDKL5-Related Disorders Sequencing and Deletion/Duplication

TO CONFIRM A DIAGNOSIS OF X-LINKED INFANTILE SPASM SYNDROME OR ATYPICAL RETT SYNDROME

Disease Overview

- Germline mutations in the cyclin-dependent kinase-like 5 (*CDKL5/STK9*) gene are associated with early-onset intractable seizures and severe developmental delay and result in a range of clinical phenotypes, including X-linked infantile spasm syndrome (ISSX) and atypical Rett syndrome.
- Individuals with germline mutations in either the *MECP2* or *CDKL5* genes may have overlapping clinical features, as both genes are involved in the same molecular pathway and exhibit similar expression patterns during development.
- Classic Rett syndrome is a severe, progressive neurodevelopmental disorder caused by germline mutations in the *MECP2* gene. Rett syndrome is characterized by rapid developmental regression and deceleration of head growth, as well as loss of speech, purposeful hand movements, and motor skills after 6 to 18 months of age.
- Atypical Rett syndrome includes the Hanefeld variant and X-linked infantile spasm syndrome (ISSX). ISSX, also known as West syndrome, is characterized by severe infantile spasms and mental retardation, lack of developmental progression, and hypsarrhythmia on EEG. The Hanefeld variant is used to describe females with early-onset epileptic seizures or infantile spasms with Rett-like features.
- Females with *CDKL5* mutations commonly present with infantile spasms or epileptic seizures within the first six months of life, a later intractable epileptic seizure disorder, mental retardation, hypotonia, and limited developmental progression.
- Males with *CDKL5* mutations may present with early-onset intractable epilepsy, severe encephalopathy, and profound mental retardation, although less severe phenotypes have been reported.

Prevalence

- The incidence of disorders associated with *CDKL5* gene mutations is unknown.
- *CDKL5* mutations are more common in females than males.

Genetics

- X-linked dominant inheritance; reported cases occur due to de novo mutations.
- At least 60 distinct pathogenic *CDKL5* mutations have been reported, the majority of which are sequence variants.
- Large deletions/duplications in the *CDKL5* gene have been reported in males and females. In one small series, three partial or complete *CDKL5* gene deletions/duplications represented half of identifiable mutations.

- Approximately 17 percent of females with early-onset epileptic seizures carry a *CDKL5* mutation.
- Genotype/phenotype correlations are not well established. Skewed X-inactivation patterns in females with *CDKL5* mutations may help explain phenotypic variability.

Indication for Ordering

To confirm a clinical diagnosis of a *CDKL5*-related disorder in individuals with infantile seizures, ISSX, *MECP2*-negative atypical Rett syndrome, autism, or mental retardation and seizure disorder.

Contraindications

- Testing for individuals with a previously identified familial *CDKL5* mutation. To test individuals for a specific *CDKL5* sequence variant, it is more cost-effective to order Familial Mutation, Targeted Sequencing (ARUP test code 2001961) and provide a copy of the lab report detailing the familial mutation.
- Prenatal testing.

Interpretation

- Identification of a known pathogenic *CDKL5* mutation in a symptomatic individual predicts the presence of a *CDKL5*-related disorder. Clinical phenotypes may vary.
- Lack of an identifiable *CDKL5* mutation in a clinically affected individual decreases, but does not exclude, a diagnosis of a *CDKL5*-related disorder. Medical management should rely on clinical findings and family history.
- *CDKL5* sequence variants of unknown clinical significance may be detected by sequencing.

Methodology

- PCR and bi-directional sequencing of the *CDKL5* coding region and intron-exon boundaries.
- Multiplex ligation-dependent probe amplification (MLPA) of the *CDKL5* gene includes all coding exons except exon 3.
- The combined clinical sensitivity of *CDKL5* sequencing and deletion/duplication testing is dependant on phenotype; 17 percent of females with early-onset epileptic encephalopathy have *CDKL5* mutations.
- Analytical sensitivity and specificity of sequencing and MLPA are 99 percent.

Limitations

- Deep intronic mutations and some regulatory region mutations are not detected.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Breakpoints of large deletions/duplications detected in *CDKL5* will not be determined.

Related Tests

- *CDKL5*-Related Disorders (*CDKL5*) Sequencing ([2004931](#))
- *CDKL5*-Related Disorders (*CDKL5*) Deletion/Duplication ([2004927](#))
- Familial Mutation, Targeted Sequencing ([2001961](#))

References

1. Archer HL, et al. *CDKL5* mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. *J Med Genet* 2006;43:729–34.
2. Evans JC, et al. Early onset seizures and Rett-like features associated with mutations in *CDKL5*. *Eur J Hum Genet* 2005;13:1113–20.
3. Mei D, et al. Xp22.3 genomic deletions involving the *CDKL5* gene in girls with early onset epileptic encephalopathy. *Epilepsia* 2010;51:647–54.
4. Nemos C, et al. Mutational spectrum of *CDKL5* in early-onset encephalopathies: a study of a large collection of French patients and review of the literature. *Clin Genet* 2009;76:357–71.
5. Russo S, et al. Novel mutations in the *CDKL5* gene, predicted effects and associated phenotypes. *Neurogenetics* 2009;10:241–50.

Test Information

2004935 *CDKL5*-Related Disorders (*CDKL5*) Sequencing and Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.