CDKL5-Related Disorders

Indications for Ordering

Confirm clinical diagnosis of a *CDKL5*-related disorder in individuals with

- Infantile seizures
- X-linked infantile spasm syndrome (ISSX)
- *MECP2*-negative atypical Rett syndrome
- Autism
- Intellectual disability with seizure disorder

Test Description

- Polymerase chain reaction (PCR) and bidirectional sequencing of *CDKL5* coding region and intron-exon boundaries
- Multiplex ligation-dependent probe amplification (MLPA) of *CDKL5* gene including all coding exons except exon 3

Tests to Consider

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

- Preferred initial test

CDKL5-Related Disorders (*CDKL5*) Sequencing 2004931

- Acceptable initial test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Prevalence – unknown; more common in females than males

Symptoms

- Most common symptoms
  - Early-onset intractable seizures
  - Infantile spasms (females)
  - Severe developmental delay/limited developmental progression
  - Hypotonia (females)
  - Severe encephalopathy (males)
- Variable clinical phenotypes associated with *CDKL5* variants
  - Skewed x-inactivation patterns in females may help explain phenotypic variability
  - ISSX
    - Also known as West syndrome
    - Severe infantile spasms
    - Intellectual disability
    - Lack of developmental progression
    - Hypsarrhythmia
  - Hanefeld variant (atypical Rett in females)
    - Early onset epileptic seizures
    - Infantile spasms and Rett-like features
- Individuals with *CDKL5* and *MECP2* variants may have overlapping clinical features
  - Classic Rett syndrome is caused by *MECP2* variants
    - Symptoms of classic Rett – rapid developmental regression, deceleration of head growth, loss of speech/purposeful hand movements/motor skills after 6-18 months of age

Genetics

Gene – *CDKL5*

Inheritance – X-linked dominant

Penetrance – 100%

De novo variants – majority of reported cases

Structure/function – involved in the same molecular pathway as *MECP2* and exhibits similar expression patterns during development

Variants – >100 pathogenic variants reported

- Majority are sequence variants
- Large deletions/duplications have been reported in males and females

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – for sequencing combined with deletion/duplication
  - Dependent on phenotype
  - ~17% for females with early-onset seizures (Archer 2006, Bahi-Buisson 2008)
- Analytical sensitivity/specificity – 99%

Results

- Negative – no variant detected
  - *CDKL5*-related disorder unlikely, but not excluded
- Positive – pathogenic variant in *CDKL5* was identified
- Sequence variants of unknown clinical significance may be detected

Limitations

- Diagnostic errors may occur due to rare sequence variations
- Not determined or evaluated
  - Deep intronic variants
  - Regulatory region variants
  - Breakpoints of large deletions/duplications

References

- Archer HL, Evans J, et al. CDKL5 mutations cause severe infantile spasms, early onset seizures, and severe mental retardation in female patients. J Med Genet. 2006;43:729-734
- Bahi-Buisson N, Nectoux J, et al. Key clinical features to identify girls with CDKL5 mutations. Brain. 2008;131:2647-2661