CDKL5-Related Disorders Testing

CDKL5-related disorders are rare developmental disorders that primarily affect females. Symptoms are variable, but may include seizures, infantile spasms, and developmental delay. Clinical presentation may overlap with MECP2-related disorders, including Rett syndrome. For more information on MECP2-related disorders, see the MECP2-Related Disorders – Classic or Atypical Rett Syndrome Consult topic.

DISEASE OVERVIEW

Prevalence
- Rare: >1,000 cases worldwide
- More common in females than males (9:1)

Symptoms
Clinical phenotypes are variable; skewed X-inactivation patterns in females may account for clinical variability.
- Features potentially overlapping with MECP2-related disorders:
  - Early-onset intractable seizures
  - Infantile spasms (females)
  - Severe developmental delay/limited developmental progression
  - Hypotonia (females)
  - Severe encephalopathy (males)
- Features of X-linked infantile spasm syndrome (ISSX) or West syndrome:
  - Severe infantile spasms
  - Intellectual disability
  - Lack of developmental progression
  - Hypsarrhythmia
- Hanefeld variant (early-onset seizure variant of atypical Rett syndrome in females)
  - Early onset epileptic seizures
  - Infantile spasms and Rett-like features

GENETICS

Gene
CDKL5 (cyclin-dependent kinase-like 5)

Inheritance
X-linked dominant

Penetrance
100%

De novo Variants
Majority of reported cases

TESTS TO CONSIDER

CDKL5-Related Disorders (CDKL5) Sequencing and Deletion/Duplication 2004935
Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification
Preferred initial test to confirm clinical diagnosis of a CDKL5-related disorder in individuals with:
- Infantile seizures
- ISSX
- Atypical Rett syndrome and negative MECP2 result
- Autism
- Intellectual disability with seizure disorder

CDKL5-Related Disorders (CDKL5) Sequencing 2004931
Method: Polymerase Chain Reaction/Sequencing
Acceptable initial test to confirm clinical diagnosis of a CDKL5-related disorder in individuals with:
- Infantile seizures
- ISSX
- Atypical Rett syndrome and negative MECP2 result
- Autism
- Intellectual disability with seizure disorder

Related Test
Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing
Recommended test for a known familial sequence variant previously identified in a family member. A copy of the family member’s lab report documenting the familial variant is REQUIRED. Consultation with a genetic counselor is advised.
Structure/Function
Involved in the same molecular pathway as the MECP2 gene 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\(^1,2\)
- Analytical sensitivity/specificity: 99%

Results
<table>
<thead>
<tr>
<th>Result</th>
<th>Findings</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Pathogenic variant detected</td>
<td>Diagnosis confirmed</td>
</tr>
<tr>
<td>Negative</td>
<td>No pathogenic variant detected</td>
<td>CDKL5-related disorder unlikely, but not excluded</td>
</tr>
<tr>
<td>Uncertain</td>
<td>Variant(s) of uncertain significance identified</td>
<td>Variant(s) may be disease causing or benign</td>
</tr>
</tbody>
</table>

Limitations
- Diagnostic errors may occur due to rare sequence variations or repeat element insertions
- Deep intronic variants, regulatory region variants, and breakpoints of large deletions/duplications are not detected or evaluated
- Single exon deletions/duplications may not be detected due to probe location

REFERENCES

RELATED INFORMATION
MECP2-Related Disorders - Classic or Atypical Rett Syndrome
Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder Laboratory Testing - Neurocognitive Impairments