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

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
- 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
Laboratory Testing for Developmental Delay, Intellectual Disability, and Autism Spectrum Disorder
Testing for Genetic Syndromes Related to Developmental Delay (DD), Intellectual Disability (ID), and Autism Spectrum Disorder (ASD)

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