CDKL5 Gene Analysis in X-linked Early Infantile Epileptic Encephalopathy (EIEE2) / Atypical Rett Syndrome / West Syndrome

Clinical Features:
X-linked early infantile epileptic encephalopathy (EIEE2) is characterized by intractable early-onset tonic seizures or spasms. This disorder is genetically heterogeneous, with up to a fifth of cases resulting from pathogenic variants in the CDKL5 gene. The majority of patients with pathogenic variants in CDKL5 causing EIEE2 are female. Females with CDKL5 variants typically present with drug-resistant seizures that begin before 6 months of age, and more than 90% show a phenotype before the end of the first year. Up to 70% of affected females develop infantile spasms (IS), often in conjunction with hypsarrythmia leading to a diagnosis of West syndrome. Less commonly, the initial clinical presentation may be characterized by autism, hypotonia, and developmental delay. Some females with CDKL5 variants have features reminiscent of Rett syndrome, including breathing dysfunction, deceleration of head growth and stereotypic hand movements. However, unlike those with Rett syndrome, patients with CDKL5 variants typically are delayed from birth and do not have normal early development followed by regression with loss of language and motor skills. An Angelman syndrome-like phenotype has also been observed in some females with CDKL5 pathogenic variants. Male individuals with a CDKL5 variants typically develop epileptic encephalopathy characterized by severe intractable seizures and intellectual disability in the absence of other signs.

Genetics:
The CDKL5 gene, also known as STK9, is located on chromosome Xp22 and encodes a serine threonine kinase that is expressed in the nervous system. It is a nuclear protein that mediates phosphorylation of the Rett syndrome-related MECP2 protein. A large number of variants have been identified in the catalytic domain of the STK9 protein.

CDKL5-related disorders are X-linked dominant pattern, although pathogenic variants typically occur de novo.

Test Methods:
Analysis is performed by bi-directional sequencing of the 21 exons and their exon/intron splice junctions of CDKL5 gene. In females sequencing cannot detect large deletions, so targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available to evaluate for a deletion or duplication of one or more exons of this gene. ExonArrayDx is also offered to detect a CDKL5 duplication in affected males with X-linked mental retardation. Any variant is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other methods, as appropriate.
Test Sensitivity:
CDKL5 pathogenic variants have been identified in 8-17% of females with early-onset seizures beginning before the age of 9 months, and the variant rate increased to 28% in females with seizure onset before the age of 3 months and infantile spasms.\(^4,9\) Additional studies indicate that 4-10% of females diagnosed with early-onset epileptic encephalopathy and 6-13% of females with a Rett-like clinical presentation will harbor a variant in the CDKL5 gene identifiable by sequencing.\(^3,10,11,13\) Whole or partial deletions of the CDKL5 gene, which are not detectable by sequence analysis in a female patient, have been identified in approximately 1% of females with early-onset seizures and 3-8% of females with a diagnosis of early-onset epileptic encephalopathy.\(^9,10,13\) In a report on 20 females with CDKL5 variants, all patients were reported to have early seizures, 75% showed autistic features, and 85% demonstrated stereotypic hand movements and/or hypotonia.\(^1\)

The sensitivity of CDKL5 sequencing in males is not well established. One study identified a CDKL5 pathogenic variant in 3/8 (~38%) of males with severe intellectual disability and early-onset intractable seizures, while another found a CDKL5 pathogenic variant in 1/56 (~2%) males who had negative ARX and MECP2 testing.\(^14,15\) However, combining data from several other small studies, no CDKL5 variant were identified in a total of 87 males with early-onset seizures, epileptic encephalopathy and/or West syndrome.\(^4,9,13\) One male patient has been reported with a contiguous gene deletion including the entire CDKL5 gene and the NHS gene associated with Nance-Horan syndrome.\(^8\) Whole or partial deletions of the CDKL5 gene would be identified by sequencing in males due to failure to amplify. Very rarely, large genomic duplications including the CDKL5 gene, which would not be detectable by sequencing, have been reported in males with X-linked mental retardation.\(^16,17\)

Variant Spectrum:
The majority of CDKL5 variants are small deletions/insertions (29%), splice site (25%), missense (21%) and nonsense variants (8%), leading to loss of protein function due to premature protein truncation or mRNA decay.\(^1-6\) In addition, large genomic deletions, duplications, or translocations (8-17%) involving sections of or the entire CDKL5 locus have been reported.\(^7,8,9,10,13\) Most CDKL5 variants are de novo.

References:
3. Rosas-Vargas H et al., J Med Genet 2008; 45: 172-178,
15. Fichou et al., Neurol 2009;73:77-78.