Genetic testing of the PRRT2 Gene in Paroxysmal Kinesigenic Dyskinesia with Infantile Convulsions (PKD/IC) and Benign Familial Infantile Seizures (BFIS)

**Disorder also known as:** Episodic kinesigenic dyskinesia (EKD) and infantile convulsions with choreoathetosis (ICCA)

**Clinical Features:**
Pathogenic variants in the PRRT2 gene can cause paroxysmal kinesigenic dyskinesia with infantile convulsions (PKD/IC, also called infantile convulsions and choreoathetosis or ICCA), isolated PKD, or benign familial infantile seizures (BFIS). PKD is characterized by involuntary movements triggered by the initiation of sudden motion or a change in the velocity of movements, such as going from walking to running. The attacks typically last only several seconds and result in dystonia, chorea, athetosis, or ballism. The involuntary movements do not cause loss of consciousness. Attacks typically begin in childhood, and the frequency gradually decreases with age. Treatment with anticonvulsants is usually effective in controlling the attacks. BFIS results in generalized tonic-clonic and complex partial seizures that typically occur in clusters between 3-24 months of age. The seizures typically resolve by age 2, and most individuals with BFIS have a good outcome and normal cognitive development. Pathogenic variants in the PRRT2 gene cause variable clinical features, even among individuals in the same family. Some individuals may experience both PKD and seizures while others exhibit PKD or seizures only.

**Genetics:**
The PRRT2 gene contains four exons that encode a proline-rich transmembrane protein of unknown function. This protein is expressed in neurons and contains two putative transmembrane domains. To date, more than 20 mutations have been identified throughout the coding region of the PRRT2 gene, including missense, nonsense, splice site, and frameshift mutations. c.649_650insC is a recurrent mutation that accounts for approximately 77-93% of all mutant alleles and has been identified in individuals with PKD/IC, BFIS, and isolated PKD from a variety of ethnic backgrounds (Meneret et al., 2012; Lee HY et al., 2012; Schubert et al., 2012). Deletions of the PRRT2 gene and the surrounding genomic region on chromosome 16p11.2 have been identified in individuals with PKD, some of whom also exhibited speech delay or learning difficulties (Dale et al., 2012; Lipton et al., 2009).

Pathogenic variants in the PRRT2 gene are inherited in an autosomal dominant manner. Gonadal mosaicism has been described (Schubert et al., 2012). The penetrance of PRRT2 pathogenic variants is estimated to be 80-90% (Schubert et al., 2012; van Vliet et al., 2012).
Test Methods:
Analysis is performed by bi-directional sequencing of the coding exons and exon/intron splice junctions of the PRRT2 gene. Any variant identified is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other methods as appropriate. Whole genome array CGH (GenomeDx) is available to evaluate for a deletion of the PRRT2 gene and surrounding genomic region.

Test Sensitivity:
The likelihood of detecting a variant in the PRRT2 gene by sequencing depends on an individual’s clinical phenotype and family history. The likelihood of detecting a large deletion is not well established.

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<tr>
<th>Phenotype</th>
<th>Familial Cases</th>
<th>Sporadic Cases</th>
<th>References</th>
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<tbody>
<tr>
<td>PKD/IC</td>
<td>62-96%</td>
<td>36%</td>
<td>Heron et al., 2012; Lee HY et al., 2012; Lee YC et al., 2012</td>
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<tr>
<td>BFIS</td>
<td>83%</td>
<td>30%</td>
<td>Heron et al., 2012; Schubert et al., 2012; Specchio et al., 2012</td>
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<tr>
<td>PKD</td>
<td>85%</td>
<td>35%</td>
<td>Meneret et al., 2012; Liu et al., 2012; Cao et al., 2012</td>
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References: