**Condition Description**

Mutations in the *PCDH19* gene (Xq22) (OMIM#: 300460) have been associated with epileptic encephalopathy, early infantile, 9 (OMIM #: 300088). In the original report, 15 related female patients had a grand mal convulsive disorder associated with intellectual disability. The reported age of onset varied from 4 to 18 months of age. Early symptoms included partial and generalized convulsions that were associated with developmental regression. The frequency of seizures was reported to decline at age of 2 but cognitive impairment was prominent in the affected females.

Other features reported in this family and other unrelated affected families include variable intellectual disability, neuropsychiatric disorders including autism and schizophrenia, purposeless hand movements, poor language development, and ataxia. Some obligate carrier males have been reported to display obsessive traits and interests.

One study identified *PCDH19* mutations in 11 of 45 (24.4%) unrelated females with epileptic encephalopathy of infancy who were negative for mutations in the *SCNIA* Gene. Another study found *PCDH19* mutations in 2 of 86 (2.3%) females with epilepsy with or without intellectual disability. A third study identified *PCDH19* mutations in 13 of 117 (11%) females with febrile seizures and epilepsy.

For patients with suspected X-Linked Epilepsy with MR, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**References:**

- OMIM# 300460: *PCDH19* gene
- OMIM# 300088: X-Linked Epilepsy with MR

**Genes**

*PCDH19*

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of *PCDH19*-Related X-Linked Epilepsy with MR.
- Carrier testing in adults with a family history of *PCDH19*-Related X-Linked Epilepsy with MR.

**Methodology**

PCR amplification of 6 exons contained in the *PCDH19* gene is performed on the patient's genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: One study identified *PCDH19* mutations in 11 of 45 (24.4%) unrelated females with epileptic encephalopathy of infancy who were negative for mutations in the *SCNIA* Gene. Another study found *PCDH19* mutations in 2 of 86 (2.3%) females with epilepsy with or without intellectual disability. A third study identified *PCDH19* mutations in 13 of 117 (11%) females with febrile seizures and epilepsy.

Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml 

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Related Tests**

- Deletion/duplication analysis of the *PCDH19* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90 genes.