ARHGEF9-related Hereditary Hyperekplexia: ARHGEF9 Gene Deletion/Duplication

**Condition Description**

Hereditary hyperekplexia (HPX) is characterized by stiffness after birth that normalizes during the first year. Infants have excessive startle reflex with a short period of generalized stiffness after an unexpected stimuli. During the period of stiffness, voluntary movements are not possible. Exaggerated head retraction reflex is observed when the tip of the nose is tapped. Additional features include periodic limb movements in sleep or while falling asleep. Sudden infant death (SIDS) has been reported by Rivera et al. Intellect is usually normal; however, mild intellectual disability may occur.

The ARHGEF9 gene (Xq22.1) is one of five genes known to be associated with HPX. It shows X-linked inheritance. Harvey et al. (2004) identified one individual with a mutation (p.G55A) in the ARHGEF9 gene from a cohort of 32 patients with HPX without mutations in the GLRA1 or GLRB2 genes. This mutation was not seen in 200 unrelated Caucasian control chromosomes. This individual was reported to have seizures as well and thus, mutations in the ARHGEF9 gene are found in patients with early infantile epileptic encephalopathy (EIEE8).

For patients with suspected HPX, 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:**

- GeneTests
- OMIM
- #300429: ARHGEF9 gene
- OMIM #300607: EIEE8

**Genes**

ARHGEF9

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of ARHGEF9-Related HPX in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of ARHGEF9-Related HPX in whom sequence analysis was negative.

**Methodology**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

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.

**Special Instructions**

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequence analysis of the *ARHGEF9* gene is available and is required before deletion/duplication analysis.
- 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.