**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.
- Carrier testing in adults with a family history of ARHGEF9-Related HPX.

**Methodology**

PCR amplification of 10 exons contained in the ARHGEF9 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: 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. 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) or ACD (yellow 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 ARHGEF9 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.