**RYR1-related Disorders: RYR1 Gene Sequencing**

**Condition Description**

**Malignant Hyperthermia Susceptibility**

Malignant hyperthermia is a disorder of calcium regulation, which results in uncontrolled skeletal muscle hypermetabolism. The presentation can vary depending on the triggering agent used (a volatile anesthetic agent alone or used with succinylcholine (a depolarizing muscle relaxant)) and environmental factors. The manifestations seen may include hypercapnia, tachycardia, hypoxemia, hyperthermia, acidosis, and rhabdomyolysis.

Two genes are known to cause malignant hyperthermia susceptibility (MHS) - *RYR1* (19q13.2) and *CACNA1S*. Mutations in the *RYR1* gene have been identified in 70-80% of individuals with confirmed MHS. Mutations in the *CACNA1S* gene have been identified in 1% of individuals with MHS. MHS is inherited in an autosomal dominant manner.

Please note that this test is for the *RYR1* gene only.

**Central Core Disease**

Central core disease (CCD) can have a wide spectrum of features but is characterized by muscle weakness than can range from mild to severe. In more common, early-onset disease, clinical findings include hypotonia and generalized weakness, delayed motor milestones, spinal deformities, high-arched palate, joint contractures, foot deformities, and congenital hip dislocation. In the rarer, later-onset disease, clinical features include mild symmetrical myopathy, mildly affected facial muscles and occasional involvement of the extracranial muscles. Mutations in the *RYR1* gene cause CCD. Most cases of CCD are inherited in an autosomal dominant manner, but CCD can also be inherited in an autosomal recessive manner. The penetrance of CCD is variable.

For patients with suspected *RYR1*-related disorders, 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:**

- GeneReviews
- OMIM #180901: *RYR1* gene
- OMIM #145600: MHS
- OMIM #117000: CCD

**Genes**

*RYR1*

**Indications**

This test is indicated for:

- Confirmation of a clinical diagnosis of *RYR1*-related disorders.
- Carrier testing in adults with a family history of *RYR1*-related disorders.

**Methodology**

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

**Detection**

Clinical Sensitivity: 70-80% in individuals with confirmed MHS. >90% in individuals with CCD. 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 RYR1 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.