RYR1-related Disorders: RYR1 Gene Sequencing

Test Code: SRYR1
Turnaround time: 6 weeks
CPT Codes: 81408 x1

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

Type: DNA, Isolated
Specimen Requirements:
- Microtainer
- 8μg

Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
Refrigerate until time of shipment in 100 ng/μL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:
- EDTA (Purple Top)
- Infants and Young Children (2 years of age to 10 years old): 3-5 ml
- Older Children & Adults: 5-10 ml
- Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:
Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Type: Saliva

Specimen Requirements:
- Oragene™ Saliva Collection Kit
- Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

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.