RYR1-related Disorders: RYR1 Gene Deletion/Duplication

Test Code: DRYR1
Turnaround time: 2 weeks
CPT Codes: 81228 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 in an individual in whom sequence analysis was negative.
- Carrier testing in adults with a family history of RYR1-related disorders 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

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.

**Special Instructions**

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

**Related Tests**

- Sequence analysis of the RYR1 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.