**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 succinylocholine (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 that 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 extracocular 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.

### 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**

**Type:** DNA, Isolated

**Specimen Requirements:**
- Microtainer
- 3µg
- Isolation using the Perkin Elmer™Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

**Specimen Collection and Shipping:**

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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.

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 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.