

## Malignant Hyperthermia Susceptibility Testing via Sequential *RYR1* Exon Sequencing

**Brief Description:** Malignant Hyperthermia (MH) is a severe adverse reaction to commonly used volatile anesthetics (halothane, sevoflurane, desflurane, enflurane, isoflurane) or to depolarizing muscle relaxants (succinylcholine). In susceptible patients these agents may trigger uncontrolled skeletal muscle hypermetabolism. In almost all cases, the first manifestations of MH occur in the operating room. Death can result unless the patient is promptly treated.

**Genetics:** MH susceptibility is inherited in an autosomal dominant manner. Mutations in the *RYR1* gene are the primary known cause of MH. The large *RYR1* (ryanodine receptor type I) gene with 106 exons encodes the skeletal muscle calcium release channel.

This particular test involves sequential DNA sequencing of all *RYR1* exons that have been reported to contain causative mutations. The test begins with sequencing of the 13 primary MH exons that contain a large fraction of mutations (see Primary MH Exon Test). If a likely causative mutation is found within these exons, the test is stopped. Otherwise, sequencing continues with the 11, 3' exons (see MH/Central Core Disease 3' Exon Test). If nothing is found in the first two panels, sequencing concludes with a final set of exons (currently 34, 42, 43, 50, 51, 67, 71). All 3 of these tests may be ordered individually. We expect to gradually expand the total number of exons tested.

**Indications for Test:** The ideal candidate for this test is a member of a family with a history of MH. The ideal candidate should also have had either a positive *in vitro* contracture test or a clear MH event. PreventionGenetics recommends that the hunt for the causative mutation begin in such a family member. Once the causative mutation is identified, then other family members can be screened at much reduced cost. Other, less ideal candidates for the test are those with just a family history of MH or those with a "MH-like" event and no family history.

**Sensitivity of Test:** Based on results from the literature, we estimate that the full sequential test will detect likely causative mutations in 50-70% of ideal test candidates. Sensitivity will be lower for other test candidates.

**MHAUS:** PreventionGenetics is working closely with the Malignant Hyperthermia Association of the U. S. ([www.mhaus.org](http://www.mhaus.org)). There is a 10% price discount for MHAUS members. MHAUS provides financial support for testing in some cases.

### SPECIMEN REQUIREMENTS

Collect a minimum of 1 ml of whole blood in EDTA (purple top tube) or ACD (yellow top tube).

Whole blood collected in Na Heparin is acceptable but not preferred.

Ship whole blood specimens at ambient temperature. Do not freeze blood tube.

During hot summer months, include a frozen ice pack in the shipping container. Do not allow the ice pack to come in direct contact with the specimen tubes. In winter, include an unfrozen ice pack to help moderate extremes in temperature. The DNA in whole blood is stable for at least 48 hours at 21°C, 5-7 days at 4°C.

### Sequential exon sequencing of the *RYR1* gene

**\$1690.00**

Molec Diag, Ascertainment 83890

Molec Diag, Isolation 83891

Molecular Diag, Amplif x 34 83898

Mutat Id By Seq, Single Seg x 34 83904

Molecular Diag, Separation 83894

Interpretation And Report 83912

The price for this test is \$790 if a mutation is found in the first panel, and \$1390 if a mutation is found in the second panel. Single exon sequencing for the presence of previously identified mutations in the *RYR1* gene will also be provided for \$230.

**Accreditation Info. CLIA ID #: 52D1027685** (expires 1/18/07) (CAP#: 7185561, AU ID: 1407125 expires 12/20/06)

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