

Malignant Hyperthermia Susceptibility, Central Core Disease, and other RYR1 Myopathies via RYR1 Gene Sequencing

Sequential Test – Test #570

Tier 1 Only – Test #571

Tier 2 Only – Test #572

Brief Description of Clinical Features: Malignant Hyperthermia (MH) (OMIM 145600) is a severe adverse reaction to commonly used anesthetics (halothane, sevoflurane, desflurane, enflurane, isoflurane) or to depolarizing muscle relaxants (succinylcholine) (Rosenberg and Dirksen, www.geneclinics.org, 2006). In susceptible patients these agents may trigger uncontrolled 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. Alternative anesthetics are available for known MH Susceptible individuals. Central Core Disease (CCD) (OMIM 117000) is a congenital myopathy characterized by moderate muscle weakness, musculoskeletal abnormalities, and characteristic histopathology (Jungbluth Orphanet J Rare Dis 2:25, 2007; Malicdan and Nishino, www.geneclinics.org, 2007). Many patients with Central Core Disease are also MH Susceptible.

Genetics: MH Susceptibility is an autosomal dominant disorder. CCD is also usually considered dominant, although recessive inheritance and allele silencing in muscle have been reported (Zhou et al. Brain 130:2024-2036, 2007; Monnier et al. Hum Mut 29:670-678, 2008). Mutations in the RYR1 gene are the primary known cause of MH and the only known cause of CCD. The RYR1 gene with 106 exons encodes the skeletal muscle calcium channel. MH and CCD causative mutations are almost entirely either missense or (rarely) in-frame deletion of one or a few amino acids (Robinson et al. Hum Mut 27:977-989, 2006). CCD may result from *de novo* mutation. Mutations in the RYR1 gene may also cause other myopathies such as Multiminicore Disease and Centronuclear Myopathy (Jungbluth et al. Neuromuscular Dis 17:338-345, 2007; Beggs and Agrawal, www.geneclinics.org, 2008; Treves et al. Cur Opin Pharmacol 8:319-326, 2008).

Description of This Particular Test: Full gene sequencing of RYR1 (Test #570) is performed in two tiers. Tier 1 involves bidirectional sequencing of exons 2, 6, 8, 9, 11, 12, 14, 15, 17, 39, 40-41, 44-47, 95, and 100-104. These 22 exons contain the great majority of conclusively documented MH and CCD causative mutations (www.emhg.org). The full coding region of each exon plus ~50 bp of flanking non-coding DNA on either side are sequenced. If a likely causative mutation is found in Tier 1, testing stops. Otherwise testing continues with the remaining 84 exons in Tier 2. Tiers 1 and 2 may be ordered separately (Tests #571 and 572, respectively).

Reference Sequences: Genomic: NC_000019.8 mRNA and protein: CCDS 33011.1

Indications for Test: Ideal MH test candidates have a family history of MH along with either a positive *in vitro* contracture test or a clear MH event. The hunt for the causative mutation should begin in such a family member. If a causative mutation is identified, 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. Tier 2 testing is not generally recommended for less ideal MH candidates. CCD test candidates are patients with myopathy and characteristic cores upon microscopic examination of skeletal muscle biopsy.

Sensitivity of Test: Based on results from both the literature and PreventionGenetics, we estimate that the full gene test will detect likely causative mutations in roughly 65% of ideal MH test candidates. Sensitivity will be lower for non-ideal MH candidates. Similarly, the full gene test will detect likely causative mutations in ~70% of patients with Central Core Disease (Wu et al. Brain 129:1470-1480, 2006).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Prices:

Tier 1 Only: Sequencing of RYR1 exons 2, 6, 8, 9, 11, 12, 14, 15, 17, 39, 40, 44-47, 95, 100-103 \$ 740

Tier 2 Only: Sequencing of the remaining 84 RYR1 exons \$ 3,790

Tiers 1 and 2: Sequencing of full RYR1 gene \$ 3,990

There is a 10% price discount for members of the Malignant Hyperthermia Association of the U.S. (www.mhaus.org).

CPT Codes:

Codes	Description	Tier 1 Only	Tier 2 Only	Tier 1 + Tier 2
83890	Ascertainment	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	DNA Isolation	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	Amplification	\$ 220 (x17)	\$ 1360 (x73)	\$ 1420 (x90)
83904	Mutation Ident by Sequencing	\$ 320 (x17)	\$ 2050 (x73)	\$ 2140 (x90)
83894	Separation	\$ 40 (x1)	\$ 160 (x1)	\$ 190 (x1)
83912	Interpretation and Report	\$ 90 (x1)	\$ 150 (x1)	\$ 170 (x1)
Totals:		\$ 740	\$ 3790	\$ 3,990

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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