



Malignant Hyperthermia Susceptibility

Synonym: Malignant Hyperpyrexia

Henry Rosenberg, MD,¹ Nyamkhishig Sambuughin, PhD,² Sheila Riazhi, MD,³ and Robert Dirksen, PhD⁴

Created: December 19, 2003; Updated: January 16, 2020.

Summary

Clinical characteristics

Malignant hyperthermia susceptibility (MHS) is a pharmacogenetic disorder of skeletal muscle calcium regulation associated with uncontrolled skeletal muscle hypermetabolism. Manifestations of malignant hyperthermia (MH) are precipitated by certain volatile anesthetics (i.e., halothane, isoflurane, sevoflurane, desflurane, enflurane), either alone or in conjunction with a depolarizing muscle relaxant (specifically, succinylcholine). The triggering substances cause uncontrolled release of calcium from the sarcoplasmic reticulum and may promote entry of extracellular calcium into the myoplasm, causing contracture of skeletal muscles, glycogenolysis, and increased cellular metabolism, resulting in production of heat and excess lactate. Affected individuals experience acidosis, hypercapnia, tachycardia, hyperthermia, muscle rigidity, compartment syndrome, rhabdomyolysis with subsequent increase in serum creatine kinase (CK) concentration, hyperkalemia with a risk for cardiac arrhythmia or even cardiac arrest, and myoglobinuria with a risk for renal failure. In nearly all cases, the first manifestations of MH (tachycardia and tachypnea) occur in the operating room; however, MH may also occur in the early postoperative period. There is mounting evidence that some individuals with MHS will also develop MH with exercise and/or on exposure to hot environments. Without proper and prompt treatment with dantrolene sodium, mortality is extremely high.

Diagnosis/testing

The diagnosis of MHS is established with in vitro muscle contracture testing by measuring the contracture responses of biopsied muscle samples to halothane and graded concentrations of caffeine. The diagnosis of MHS can also be established by identification of a pathogenic variant in *CACNA1S*, *RYR1*, or *STAC3* on molecular genetic testing.

Author Affiliations: 1 President, Malignant Hyperthermia Association of the United States Sherburne, New York; Email: henryrosenberg@yahoo.com. 2 Adjunct Associate Professor, Department of Military and Emergency Medicine Uniformed Services University Senior Scientist, Henry M Jackson Foundation Bethesda, Maryland; Email: nyamkhishig.sambuughin.ctr@usuhs.edu. 3 Associate Professor, Department of Anesthesia University of Toronto Toronto, Ontario; Email: sheila.riazi@uhn.ca. 4 Professor, Department of Pharmacology and Physiology University of Rochester Medical Center Rochester, New York; Email: robert_dirksen@urmc.rochester.edu.

Management

Treatment of manifestations: Early diagnosis of an MH episode is essential. Successful treatment of an acute episode of MH includes: discontinuation of potent inhalation agents and succinylcholine; increase in minute ventilation to lower end-tidal CO₂; use of MHAUS helpline; administration of dantrolene sodium intravenously; cooling measures if body temperature is >38.5° C; treatment of cardiac arrhythmias if needed (do not use calcium channel blockers); monitoring blood gases, serum concentrations of electrolytes and CK, blood and urine for myoglobin, and coagulation profile; treatment of metabolic abnormalities.

Prevention of primary manifestations: Individuals with MHS should not be exposed to potent volatile agents and succinylcholine. Individuals undergoing general anesthetics that exceed 30 minutes in duration should have their temperature monitored using an electronic temperature probe. Individuals with MHS should carry proper identification as to their susceptibility.

Agents/circumstances to avoid: Avoid potent inhalation anesthetics and succinylcholine. Calcium channel blockers should not be given together with dantrolene because of a potential cardiac depressant effect. Serotonin antagonist (5HT₃-antagonist) antiemetics should be used cautiously. Individuals with MHS should avoid extremes of heat, but not restrict athletic activity unless there is a history of overt rhabdomyolysis and/or heat stroke. Strenuous activities at high ambient temperatures should be avoided or performed with caution. In individuals with MH undergoing cardiac bypass surgery, aggressive rewarming should be avoided, as it may be associated with development of clinical signs of MH.

Evaluation of relatives at risk: If the MHS-causative pathogenic variant in the family is known, molecular genetic testing can be used to establish increased risk of MH in a heterozygous individual; molecular genetic testing alone cannot be used to identify family members who are not at increased risk for MH because of other possible genetic risk factors. If the pathogenic variant in the family is not known or if an at-risk relative is found to be negative for a familial pathogenic variant, muscle contracture testing can be used to assess susceptibility to MH.

Pregnancy management: If a pregnant woman with MHS requires a non-emergent surgery, a non-triggering anesthetic (local, nerve block, epidural, spinal anesthesia, or a total intravenous general anesthetic) should be administered. Continuous epidural analgesia is highly recommended for labor and delivery. If a cesarean delivery is indicated in a woman who does not have an epidural catheter in place, neuraxial (spinal, epidural, or combined spinal-epidural) anesthesia is recommended (if not otherwise contraindicated). If a general anesthetic is indicated, a total intravenous anesthetic technique should be administered, with an anesthesia machine that has been prepared for an MH-susceptible individual.

Genetic counseling

Malignant hyperthermia susceptibility (MHS) is an autosomal dominant disorder. Most individuals diagnosed with MHS have a parent with MHS, although the parent may not have experienced an episode of MH. The proportion of individuals with MHS caused by a *de novo* pathogenic variant is unknown. Each child of an individual with MHS has a 50% chance of inheriting a causative pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if there is a known MH pathogenic variant in the family.

Diagnosis

Consensus guidelines for the diagnosis and management of malignant hyperthermia susceptibility (MHS) have been published [Glahn et al 2010, Larach et al 2012, Hopkins et al 2015, Riazi et al 2018].

Suggestive Findings

MHS **should be suspected** in individuals presenting with clinical findings summarized in Table 1. The findings relate to signs occurring during or shortly after general anesthesia.

Each clinical finding is weighted as to significance in being associated with MHS as determined by malignant hyperthermia (MH) experts using a Delphi method. Points are assigned according to weight and are then totaled to produce a raw score, which translates to a likelihood of MH score, ranging from a raw score of 0 (MH rank 1: almost never/very unlikely) to a raw score ≥ 50 (MH rank 6: almost certain) [Larach et al 1994]. The more criteria an individual fulfills, the more likely that an MH episode has occurred. For example, with only temperature elevation during anesthesia, an individual is not likely to be susceptible to MH. A limitation of the scoring system is that not every clinical finding may be measured (e.g., arterial blood gas); MH may also be recognized very quickly and treated before all the signs appear.

Table 1. Criteria Used in the Clinical Grading Scale for Malignant Hyperthermia

Clinical Finding (Maximum Score) ¹	Manifestation ²
Respiratory acidosis (15)	End-tidal CO ₂ >55 mm Hg, PaCO ₂ >60 mm Hg
Cardiac involvement (3)	Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation
Metabolic acidosis (10)	Base deficit >8 mEq/L, pH <7.25
Muscle rigidity (15)	Generalized rigidity, severe masseter muscle rigidity
Muscle breakdown (15)	Serum creatine kinase concentration >20,000/L units, cola-colored urine, excess myoglobin in urine or serum, plasma [K ⁺] >6 mEq/L
Temperature increase (15)	Rapidly increasing temperature, T >38.8° C
Other	Rapid reversal of MH signs with dantrolene (score=5), elevated resting serum creatine kinase concentration (score=10)
Family history (15)	Consistent with autosomal dominant inheritance

From Larach et al [1994], Rosenberg et al [2015]

1. Clinical findings (except family history) are in order of relative importance.

2. Signs occurring during or shortly after general anesthesia in the untreated individual

Indications for Muscle Biopsy and Contracture Testing to Confirm the Diagnosis in a Proband *

Definite indications

- Proband with a suspected clinical history of MH
- First-degree relative of a proband with a clinical history of MH, if the proband cannot be tested (e.g., too young, too old, MH death, not willing to undergo the muscle biopsy, no test center available)
- At-risk family members when the MH-causing variant is not known
- Severe masseter muscle rigidity along with generalized rigidity during anesthesia with MH-triggering agents
- Isolated masseter muscle rigidity with succinylcholine
- Limited masseter muscle rigidity along with rhabdomyolysis and/or elevated plasma CK level (hyperCKemia)
- Military service. The military requires determination of MH susceptibility by contracture testing in persons with a suspected personal or known family history of MH because individuals with MHS are not eligible for military service.

Possible indications. Debate exists as to other indications for diagnostic MH muscle biopsy. Some experts believe that individuals who experience any one of the following signs should undergo biopsy, following careful discussion of the pros and cons of the test:

- Postoperative rhabdomyolysis and marked elevation of serum CK concentration without other signs of classic MH
- Exercise-related rhabdomyolysis in the absence of a known myopathy

Not recommended

- Weight less than about 20 kg or age younger than five years
- Diagnosis of neuroleptic malignant syndrome or serotonin syndrome

* Because contracture testing is available on a limited basis, some physicians consider all individuals with a suspected history of MH as MH susceptible and avoid anesthetic agents known to trigger MH. Although this strategy is useful, it does not provide guidance and specific answers to family members and limits the anesthetic options for the individual and family. Details regarding MH muscle biopsy centers can be obtained from the Malignant Hyperthermia Association of the US website (www.mhaus.org).

Indications for Molecular Genetic Testing

(See Establishing the Diagnosis, Note.)

- Confirmed clinical episode of MH
- Positive caffeine/halothane contracture test
- High likelihood of having experienced an MH episode, as determined by biopsy center/hotline consultants, and/or likely MH based on the Clinical Grading Scale (See Table 1.)
- Relative with a positive contracture test or a known MH-causing variant
- Unexplained death with signs of MH during or immediately after anesthesia
- Exercise-related rhabdomyolysis and/or heat stroke

Establishing the Diagnosis

The diagnosis of MHS is **established** in a proband with:

- A positive diagnostic contracture test **OR**
- A heterozygous pathogenic variant in one of the genes listed in Table 3 identified by molecular genetic testing.

Note: (1) Molecular genetic testing is not 100% sensitive; MHS cannot be excluded based on failure to identify a pathogenic variant in one of the genes listed in Table 3. In such cases contracture testing should be performed at an MH muscle biopsy center. (2) A variant is established as pathogenic through variant assessment that includes functional analysis (see Molecular Genetics).

Contracture Test

Since the mid-1970s, the standard diagnostic test for MHS has been the in vitro measurement of contracture response of biopsied muscle to graded concentrations of caffeine and the anesthetic halothane. The test is referred to as the **caffeine/halothane contracture test (CHCT)** in North America and the **in vitro contracture test (IVCT)** in Europe and elsewhere. (Note: The calcium-induced calcium release test is used only in Japan, and no international standards exist.)

- The test must be performed on a biopsy of approximately 2.0 g of muscle from the vastus lateralis or medialis (some centers have used biopsies from other muscle groups, but the test has only been

standardized for the vastus muscle group) within five hours of harvesting. Usually, the individual must be at an MH diagnostic center in order to undergo testing.

- The individual is anesthetized with general anesthesia, spinal anesthetic or with a femoral nerve block or one of its variants:
 - Direct muscle infiltration with local anesthetic is contraindicated because it could affect tissue viability.
 - In all cases, the anesthetic drugs used must be safe for MH-susceptible individuals.
- The surgeon must not use electrocautery or stretch the muscle.

Muscle bundles weighing 100-150 mg are mounted in a chamber containing buffered solution and, after a period of stabilization, are caused to contract with supramaximal electrical stimuli. The isometric contracture that develops following exposure to pharmacologic agents that cause sarcoplasmic reticulum calcium release (e.g., halothane, caffeine, and ryanodine) is measured.

The two versions of the testing protocol with international standards of test performance and interpretation are the North American [Litman & Rosenberg 2005] and the European versions [Hopkins et al 2015]. The essential differences are: (1) the North American protocol utilizes exposure to 3% halothane, while the European version utilizes incremental exposure to halothane; and (2) the North American version requires testing of three muscle bundles for each drug, whereas the European version requires testing of two muscle bundles for each drug (see Table 2).

Table 2. Testing Protocols for Malignant Hyperthermia

Designation	North American Protocol ¹	Designation	European Protocol ²
MHS	<ul style="list-style-type: none"> • Contracture of ≥ 0.7 g to 3% halothane; OR • Contracture of ≥ 0.3 g to 2.0 mmol/L caffeine 	MHS _{hc}	<ul style="list-style-type: none"> • Contracture of ≥ 0.2 g to $\leq 2\%$ halothane; AND • Contracture of ≥ 0.2 g to ≤ 2.0 mmol/L caffeine
MHS	Contracture to: <ul style="list-style-type: none"> • Halothane only; OR • Caffeine only 	MHS _h ³ or MHS _c ³	Contracture to: <ul style="list-style-type: none"> • Halothane only; OR • Caffeine only
MHN	<ul style="list-style-type: none"> • No contracture; OR • Contracture of < 0.7 g to halothane; OR • Contracture of < 0.3 g to 2.0 mmol/L caffeine 	MHN	No significant contractures to either agent

MHN = malignant hyperthermia negative; MHS = malignant hyperthermia susceptible; MHS_c = malignant hyperthermia susceptible with contracture after caffeine exposure; MHS_h = malignant hyperthermia susceptible with contracture after halothane exposure; MHS_{hc} = malignant hyperthermia susceptible with contracture after halothane exposure and after caffeine exposure

Note: (1) Studies to determine the sensitivity and specificity of the contracture test show that both protocols have a sensitivity of about 100%. Specificity is generally between 80% and 97%, according to several studies with these protocols [Allen et al 1998]. (2) Some laboratories employ 1.0 or 2.0 $\mu\text{mol/L}$ ryanodine or 4-chloro-m-chlorocresol in addition to halothane and caffeine to clarify equivocal results.

1. In the North American protocol, most centers report results as MHS or MHN.

2. Hopkins et al [2015]

3. MHS_c and MHS_h are both considered MHS.

Molecular Genetic Testing: Recommended Tier 1

When the clinical and laboratory findings suggest the diagnosis of MHS, molecular genetic testing approaches should include use of a **multigene panel**. A MHS multigene panel that includes *CACNA1S*, *RYR1*, *STAC3*, and

other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Molecular Genetic Testing: Tier 2

Comprehensive genomic testing (when available) including exome sequencing and genome sequencing may be considered if gene-targeted testing did not identify a pathogenic variant in an individual with a positive contracture test.

Exome sequencing is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

Table 3. Molecular Genetic Testing Used in Malignant Hyperthermia Susceptibility (MHS)

Gene ^{1, 2}	Proportion of MHS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants ³ Detectable by Method	
		Sequence analysis ⁴	Gene-targeted deletion/duplication analysis ⁵
<i>CACNA1S</i>	~1% ⁶	~100%	Unknown ⁷
<i>RYR1</i>	50%-60% ⁸	~100%	2 families ⁹
<i>STAC3</i>	<1% ¹⁰	~100%	Unknown ⁷
Unknown ¹¹	Up to 40%	NA	

1. Genes are listed in alphabetic order.

2. See Table A. Genes and Databases for chromosome locus and protein.

3. See Molecular Genetics for information on allelic variants detected in this gene.

4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

6. Monnier et al [1997], Stewart et al [2001]

7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

8. Sambuughin et al [2005], Galli et al [2006], Robinson et al [2006], Kraeva et al [2011]

9. Sambuughin et al [2001a]

10. Horstick et al [2013], Zaharieva et al [2018]

11. Up to 30% of individuals with MHS do not have an identified pathogenic variant in any of the genes in Table 1. MHS has been linked to 17q11.2-q24, 3q13.1, 5p, and 7q21-q22; however, no additional MH-related candidate genes have been identified.

Clinical Characteristics

Clinical Description

The manifestations of malignant hyperthermia (MH) result from exposure to certain volatile anesthetic agents (i.e., halothane, isoflurane, sevoflurane, desflurane, and enflurane) that act as triggers either alone or in conjunction with succinylcholine, a depolarizing muscle relaxant. MH is an inherited pharmacogenetic disorder of calcium regulation resulting in uncontrolled skeletal muscle hypermetabolism [Rosenberg et al 2015] with variable clinical presentations (depending on the triggering agents and environmental factors, such as metabolic state and body temperature) at the beginning of anesthesia.

The triggering substances initiate uncontrolled release of calcium from the sarcoplasmic reticulum via the skeletal muscle calcium release channel (RyR1), and also may promote entry of extracellular calcium into the myoplasm leading to the sustained pathologic increase in cytosolic calcium in skeletal muscle cells [Yang et al 2007, Duke et al 2010, Riazi et al 2018]. Increased myoplasmic calcium causes contracture of skeletal muscles and activates glycogenolysis and cell metabolism, resulting in excessive production of heat and excess lactate. Activation of the oxidative cycle leads to high oxygen consumption and high carbon dioxide production.

MH clinical manifestations are variable; with prompt and rapid clinical response, some signs may not appear. Hypercapnia is common, as is tachycardia. Hyperthermia may be one of the early signs of MH. However, failure to monitor core temperature may lead to a delay in detecting hyperthermia. Skin temperature measurement is often misleading during MH crises [Larach et al 2010]. Acidosis may be mild if the syndrome is recognized and treated promptly. HyperCKemia and rhabdomyolysis are more common when succinylcholine has been used but may be mild or not appear at all in some individuals, for reasons that are not clear. In some instances rhabdomyolysis does not appear for several hours. Hyperkalemia, leading to cardiac arrhythmia and even arrest, is uncommon if the syndrome is detected and treated promptly but may develop with remarkable rapidity.

In survivors, normalization of edematous muscle and serum CK concentration occurs within ten to 15 days, but symptom resolution may take longer (Figure 1) [Jurkat-Rott et al 2000].

MH may appear at any point during anesthetization or within an hour or so after termination of anesthesia. If succinylcholine is used during induction of anesthesia, an acceleration of the manifestations of MH may occur; tachycardia, elevation of end-tidal carbon dioxide levels, hypertension, marked temperature elevation, and arrhythmias are seen over the course of five to ten minutes. However, a completely normal response to succinylcholine may be present in some individuals susceptible to MH; in these individuals, a potent inhalation agent is apparently necessary to trigger the syndrome.

In almost all instances, the first manifestations of MH occur in the operating room. In classic MH, the initial signs are tachycardia, rapidly rising end-tidal CO₂, and tachypnea. Tachypnea is usually not recognized because most individuals receiving general anesthesia are paralyzed. Shortly after the heart rate increases, the blood pressure may increase, often associated with ventricular arrhythmias induced by sympathetic nervous system stimulation from hypercarbia, hyperkalemia, and catecholamine release. Thereafter, muscle rigidity or increased muscle tone may become apparent; and body temperature increases at a rate of 1°-2° C every five minutes.

At the same time, the CO₂ absorbent used in general anesthesia becomes activated and warm to the touch from the exothermic reaction with the CO₂ exhaled by the affected individual. The individual may display peripheral mottling, on occasion sweating, and in rare cases cyanosis. Blood gas analysis usually reveals hypercarbia (P_{CO₂}>60 mm Hg) and respiratory and metabolic acidosis without oxygen desaturation. Elevation of end-tidal CO₂ greater than 55 mm Hg is one of the earliest signs of MH; however, vigorous mechanical hyperventilation may prevent hypercarbia and delay the diagnosis [Karan et al 1994]. A mixed venous blood sample shows even more evidence of CO₂ retention and metabolic acidosis. Hyperkalemia, hypercalcemia, lactic acidemia, and

myoglobinuria are characteristic but not always present. Increase in serum CK concentration often exceeds 20,000 units/L in the first 12-24 hours.

Death results unless the individual is promptly treated (see Management). Even with treatment and survival, the individual is at risk for life-threatening myoglobinuric renal failure, disseminated intravascular coagulation (DIC), compartment syndrome, and recrudescence of the syndrome within the first 24-36 hours following the episode. A study of MH using a North American MH registry containing information about affected individuals reported between 1987 and 2006 showed that nonfatal complications occurred in 35% of these individuals. Twelve of these complications included cardiac, renal, or hepatic dysfunction; coma or change in consciousness level; pulmonary edema; and DIC [Larach et al 2010].

Early diagnosis and rapid therapy are life saving and also lead to a reduction of clinical symptoms. It should be noted that modern anesthetic care and monitoring often allow early detection of MH. Treatment with dantrolene results in much lower morbidity and mortality than first reported when MH was recognized in the 1960s [Larach et al 2008]; however, mortality may be as high as 11% [Rosero et al 2009]. The likelihood of any complication increased 2.9 times per 2° C increase in maximum temperature and 1.6 times per 30-minute delay in dantrolene administration [Larach et al 2010]. The most frequent complications associated with dantrolene administration are muscle weakness (14.6%), phlebitis (9.2%), and gastrointestinal upset (4.3%). There is a 25% increase in the risk for any of the above complications when the total dose of dantrolene as required by clinical indications is twice the recommended initial treatment dose of 2.5 mg/kg [Brandom et al 2011].

The presentation of MH outside a hospital setting may pose special problems. Several deaths from MH have occurred when the episode began in an ambulatory surgery setting. Probable causes include inadequate preparation for treating MH (including absence of dantrolene), insufficient and unprepared personnel, and problems in stabilizing an affected individual prior to transfer to a hospital. It is suggested that all facilities have a plan to deal with MH and hold practice drills at regular intervals (see Larach et al [2012] for transfer-of-care protocols).

MH may also occur in the early postoperative period, usually within the first hour of recovery from anesthesia. Characteristic tachycardia, tachypnea, hypertension, and arrhythmias presage an episode of MH. Isolated myoglobinuria without an obvious increase in metabolism in the postoperative period (≤ 24 hours) should alert the anesthesiologist to the possibility of MH.

Of note, an MH episode may not occur with every exposure to "trigger" agents; clinical manifestations depend on genetic predisposition, dose of trigger agents, and duration of trigger exposure.

Signs of MH have also been reported without exposure to anesthetic agents. In some cases signs follow overdose of MDMA agonists; in other cases MH may be associated with heat and exercise.

Environmental/Exertional Heat Stress

Recent clinical, genetic, and laboratory studies using animal models provide evidence for a relationship between environmental or exertional heat stress (EHS) and MHS [Chelu et al 2006, Yang et al 2006, Durham et al 2008, Lanner et al 2012]. Some individuals who have experienced exertional heat illness have been found to be MH susceptible based on contracture testing [Capacchione & Muldoon 2009]. In one study, one third of young military recruits who experienced exercise-induced heat illness had an abnormal contracture response.

Evidence of a relation between EHS and MHS is presented by Tobin et al [2001] in the case report of a boy age 12 years who died from an MH-like event following participation in a football game. The boy had recovered from a previous clinical MH episode during general anesthesia with sevoflurane; sequence analysis revealed that both the boy and his father had a common *RYR1* pathogenic variant (p.Arg163Cys). A more recent study found that two unrelated children who experienced fatal non-anesthetic awake episodes triggered by either a viral

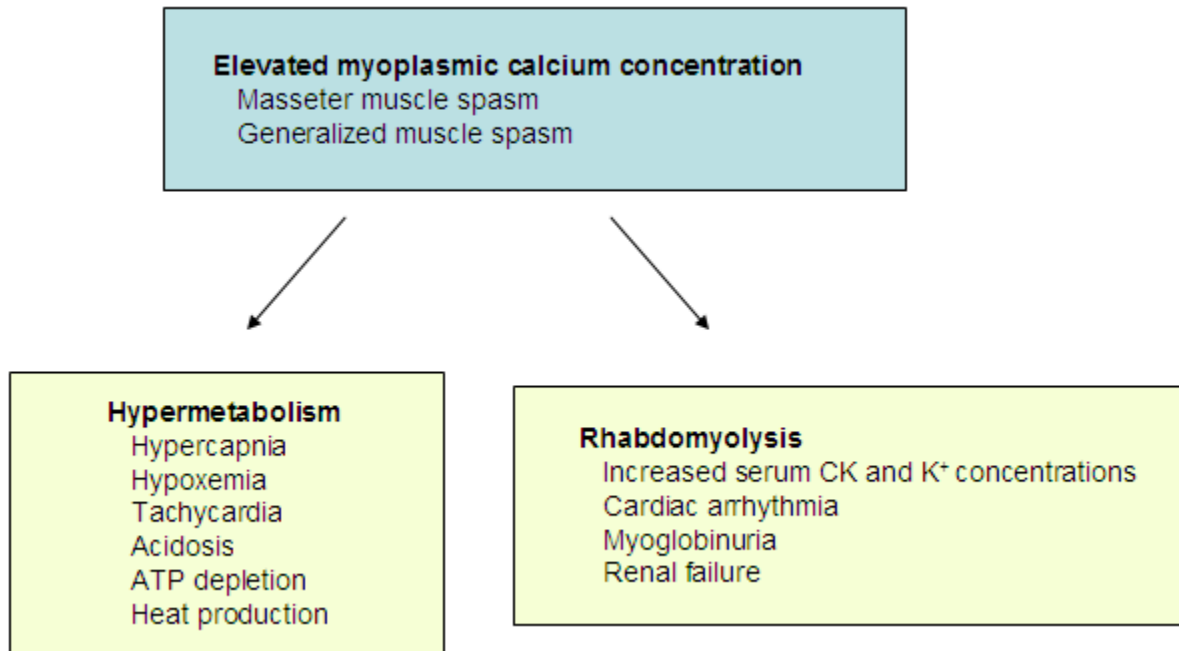


Figure 1. Clinical features of malignant hyperthermia susceptibility

Note: Early diagnosis and rapid therapy are both life saving and lead to a reduction of clinical symptoms.

Adapted from Jurkat-Rott et al [2000]

prodrome or exposure to environmental heat stress possessed an identical *RYR1* variant (p.Arg3983Cys), while one of the children also had a second variant (p.Asp4505His) [Groom et al 2011].

MHS Phenotypes

Several distinct *RYR1*-related myopathies can predispose to classic MH:

- **Central core disease** (OMIM 117000) and **multiminicore disease** (OMIM 255320) are myopathies caused by mutation of *RYR1*. Muscle weakness can range from mild to severe. Most affected individuals have mild disease with symmetric proximal muscle weakness & variable involvement of facial & neck muscles. Motor development is usually delayed, but most affected individuals acquire independent ambulation. Severe disease is early in onset with profound hypotonia often accompanied by poor fetal movement, spinal deformities, hip dislocation, joint contractures, poor suck, and respiratory insufficiency requiring assisted ventilation. Multiminicore disease is broadly classified into four groups: classic form, moderate form with hand involvement, antenatal form with arthrogryposis multiplex congenita, and ophthalmoplegic form. About 75% of affected individuals have classic symptoms characterized by neonatal hypotonia, delayed motor development, and axial muscle weakness, which leads to development of scoliosis and significant respiratory involvement; varying severity of spinal rigidity is present. Each of the other three forms is seen in fewer than 10% of individuals.
- **King or King-Denborough syndrome** (OMIM 145600) is characterized by: distinctive facies, ptosis, downslanted palpebral fissures, widely spaced eyes, epicanthal folds, low-set ears, malar hypoplasia, micrognathia, high-arched palate, clinodactyly, single palmar crease, *pectus excavatum*, winging of the scapulae, lumbar lordosis, and mild thoracic scoliosis. Individuals present with hypotonia at birth, slightly delayed motor development, diffuse joint hyperextensibility, and mild proximal muscle weakness. Muscle biopsy reveals minimal but identifiable changes represented by fiber size variability, type I fiber predominance and atrophy, perimysial fibrous infiltration, and some disarray of the intermyofibrillary

network. Pathogenic variants in *RYR1* have been found in some individuals with King-Denborough syndrome.

- **STAC3 disorder (Native American myopathy)**, caused by biallelic pathogenic variants in *STAC3*, is characterized by congenital myopathy and musculoskeletal involvement of the trunk and extremities. Most children have weakness with myopathic facies, progressive kyphoscoliosis, and contractures. Other common findings are palatal anomalies (including cleft palate) and short stature. Risks for MHS and restrictive lung disease are increased. Intellect is typically normal.

Other *RYR1* allelic conditions associated with MH susceptibility:

- Vladutiu et al [2011] revealed that variants in *RYR1* may contribute to the underlying genetic risk for non-anesthesia-induced myopathies, such as statin-induced myopathy.
- In a study of 12 young men with exercise-induced rhabdomyolysis (ER), ten were determined to be MH susceptible on contracture testing and three had known MHS *RYR1* pathogenic variants [Wappler et al 2001]. In addition, the two *RYR1* pathogenic variants p.Arg401Cys and p.Arg614Cys are associated with MHS, EHS, and ER [Davis et al 2002].
- *RYR1* variants have also been found to underlie ER in African American men [Sambuughin et al 2009]. This study identified three novel *RYR1* variants: p.Ala933Thr, p.Gly2160Ser, and p.Thr4294Met, in individuals with ER.
- Retrospective data on Canadian individuals with MHS and ER showed that an *RYR1* or *CACNA1S* pathogenic variant was identified in three of 17 individuals [Kraeva et al 2017].

Genotype-Phenotype Correlations

Genotype-phenotype correlations in MHS are difficult to study. No correlation between genotype and clinical phenotype is apparent because caffeine/halothane contracture test / in vitro contracture test results are variable among diagnostic laboratories, and clinical episodes of MHS that fulfill all criteria are rare because of successful intervention during anesthetic complications.

A limited number of studies have addressed genotype-phenotype correlations in individuals with *RYR1*-related MHS [Robinson et al 2002, Robinson et al 2003, Carpenter et al 2009]. Stronger contractures and shorter response times in the response to caffeine have been reported in individuals with an *RYR1* pathogenic variant [Carpenter et al 2009].

No genotype-phenotype correlations for *STAC3* have been identified.

No genotype-phenotype correlations for *CACNA1S* have been identified.

Penetrance

In a multicenter case-control study, the overall penetrance for *RYR1*-related MHS was 40.6%. The probability of developing MH on exposure to triggers was 0.25 among all individuals with an *RYR1* pathogenic variant and 0.76 in survivors of MH reactions (95% CI of the difference 0.41 to 0.59) [Ibarra Moreno et al 2019].

Prevalence

The incidence of MH is best described by the reported incidence per anesthetic. The estimates of the incidence range from one in 3,000 anesthetics to one in 50,000 anesthetics, with most estimating an incidence in children of about one in 10,000 anesthetics and in adults of one in 50,000 anesthetics. The prevalence of MH in individuals undergoing surgery in New York state hospitals was estimated at 1:100,000 for adults [Brady et al 2009] and 3:100,000 for children [Li et al 2011]. Because many individuals who experience marked hyperthermia while undergoing surgery may be coded as being MH susceptible, the exact incidence and

prevalence has been difficult to clarify. It appears certain that there are more than 1,000 cases of MH in the US each year [Brandom & Muldoon 2004]. The incidence varies depending on the routine use of trigger anesthetics.

Gonsalves et al [2013] identified a prevalence of 0.46% (4/870) for MHS-related *RYR1* pathogenic variants. Based on genetic variation data of more than 60,000 individuals (gnomad.broadinstitute.org; accessed 6-1-22), the combined prevalence of MHS-related *RYR1* pathogenic variants was estimated at 1:2750 [Riazi et al 2018]. Using *RYR1* and *CACNA1S* genomic databases, the estimated prevalence of an MHS-related pathogenic variant was 1:1556 [Mungunsukh et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *RYR1* or *STAC3*.

Table 4. *CACNA1S*: Allelic Disorders

Gene	MOI	Disorder/ Condition	Clinical Features
<i>CACNA1S</i>	AD	Hypokalemic periodic paralysis ¹	<p>2 forms of HypoPP are recognized: paralytic form & myopathic form w/a slowly progressive fixed myopathy:</p> <ul style="list-style-type: none"> Paralytic form: attacks of reversible flaccid paralysis w/concomitant hypokalemia usually → paraparesis or tetraparesis but sparing respiratory muscles & heart. Triggering factors: mainly carbohydrate-rich meals & rest after exercise Myopathic form: → progressive fixed muscle weakness that begins as exercise intolerance (predominantly in lower limbs) at extremely variable ages; occurs independent of paralysis & may be sole manifestation of disease

AD = autosomal dominant; HypoPP = hypokalemic periodic paralysis; MOI = mode of inheritance

1. The two reports suggesting a relationship between hypokalemic periodic paralysis and malignant hyperthermia are not widely accepted because both lack adequate data to support the association [Marchant et al 2004, Parness et al 2009].

Differential Diagnosis

Malignant hyperthermia (MH). The combination of hypercarbia, muscle rigidity, tachycardia, hyperthermia, metabolic acidosis, and rhabdomyolysis during or shortly after anesthesia is distinctive for MH. Some conditions share elements of MH (see Tables 5a and 5b).

Table 5a. Acquired Conditions to Consider in the Differential Diagnosis of Malignant Hyperthermia (MH)

Condition	Features	Comment
Sepsis	Hyperthermia, hypercarbia, & acidosis	Rigidity & marked ↑ of serum CK concentration are uncommon; leukocytosis (typically present w/sepsis) is uncommon in MH.
Overheating from aggressive heating measures used w/anesthesia (esp in pediatric population)	Hyperthermia, tachycardia, & sometimes acidosis	
Pheochromocytoma crisis	Hypertension, tachycardia, & sometimes fever; may be mistaken for MH, esp in postoperative period	Heart failure may result from unopposed alpha activity if beta blockade is used to treat tachycardia.

Table 5a. continued from previous page.

Condition	Features	Comment
Ischemic encephalopathy	Manifests by failure to awaken from anesthesia, muscle rigidity sometimes progressing to opisthotonus, hyperthermia, & tachycardia	Seizures are common in ischemic encephalopathy but not in MH.
Ascending tonic-clonic syndrome	Ascending tonic-clonic activity occurs when agent ascends into the cerebral ventricles leading to frank seizures, rigidity accompanied by fever, & acidosis if respiration is compromised	Follows intrathecal injection of a water-soluble, high ionic radiologic contrast agent
Thyrotoxicosis	Hyperthermia, hypercarbia, & tachycardia	Not assoc w/muscle rigidity
Neuroleptic malignant syndrome (NMS)	Shares all features of MH incl muscle rigidity, rhabdomyolysis, acidosis, & fever	Manifests after administration of neuroleptic agents such as atypical antipsychotics, haloperidol, & drugs used in treatment of schizophrenia ¹ ; occurs in the non-anesthetized individual
Serotonin syndrome	Signs similar to NMS	Rare reaction from serotonin uptake inhibitor drugs; occurs in the non-anesthetized individual

1. Postmortem high-resolution melting followed by sequencing of selected exons of *RYR1* in 11 individuals who died of NMS revealed two pathogenic variants, one of which had previously been reported in individuals with MH [Sato et al 2010].

Table 5b. Heritable Myopathies to Consider in the Differential Diagnosis of Malignant Hyperthermia

Condition	Gene	MOI	Comment
Dystrophinopathy (Duchenne or Becker muscular dystrophy)	<i>DMD</i>	XL	Following administration of succinylcholine or potent volatile anesthetics, affected individuals are at ↑ risk for rhabdomyolysis & life-threatening hyperkalemia w/cardiac arrest. ¹
Myotonic dystrophy type 1	<i>DMPK</i>	AD	Following succinylcholine administration, can be assoc w/muscle rigidity mimicking MH
Myotonic dystrophy type 2	<i>CNBP</i>	AD	
Myotonia congenita	<i>CLCN1</i>	AR AD	

AD = autosomal dominant; AR = autosomal recessive; MH = malignant hyperthermia; MOI = mode of inheritance; XL = X-linked

1. Although these adverse events were first believed to represent a form of MH, it now appears that the pathophysiology of the hyperkalemic episodes differs from that of MH in many respects, although elevation of intracellular calcium concentration is probably common to both syndromes [Hayes et al 2008, Betzenhauser & Marks 2010].

Rhabdomyolysis

- Succinylcholine may cause rhabdomyolysis that is not obvious on cursory physical examination in individuals who have any of the myotonic syndromes or dystrophinopathy.
- Rhabdomyolysis may occur in the perioperative period in some individuals taking inhibitors of cholesterol formation [Turan et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with malignant hyperthermia susceptibility (MHS), the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with Malignant Hyperthermia Susceptibility

System/Concern	Evaluation
MH acute episode	<ul style="list-style-type: none"> • Arterial blood gas analysis • Measurement of serum electrolytes (Na, K, Cl) • Lactate • Measurement of serum CK concentrations until normalized • Coagulation studies (INR, PTT, D-dimer) • Urine myoglobin • Serum myoglobin concentration • Liver function tests (AST, ALT, alkaline phosphatase, bilirubin) • Continuous core temperature monitoring until episode resolves
Neuromuscular	Neurologic assessment for evidence of muscle damage
Other	Consultation w/clinical geneticist &/or genetic counselor

Treatment of Manifestations

For management guidelines, see Guidelines / Consensus Statements and Figure 2 [Litman & Rosenberg 2005, Glahn et al 2010, Hopkins et al 2015, Hopkins et al 2018, Riazi et al 2018].

Early diagnosis of MH, together with the administration of dantrolene sodium, is essential in the successful treatment of an acute episode of MH:

- Discontinue use of potent inhalation agents and succinylcholine.
- Increase minute ventilation to lower end-tidal CO₂.
- Get help. One resource is the Malignant Hyperthermia Association of the US (MHAUS) hotline for acute cases: 800-MH-HYPER (800-644-9737). Similar hotlines exist in other countries, specifically the UK, Germany, and Brazil.
- Prepare and administer dantrolene: 2.5 mg/kg initial dose. Tachycardia, hypercarbia, and muscle rigidity respond rapidly; multiple doses of dantrolene may be needed. The suggested upper limit is 10 mg/kg; however, more may be given as needed. Continue dantrolene at 1.0 mg/kg every four to eight hours for 24-48 hours, titrating to the desired effect (resolution of hyperthermia, acidosis, and myoglobinemia). Dantrolene sodium is a hydantoin molecule that binds to a specific region of the ryanodine receptor 1 channel. It decreases the uncontrolled release of intracellular calcium [Paul-Pletzer et al 2002]. The toxicity profile of dantrolene, when administered acutely, is extremely benign. Calcium channel blocking agents should not be administered with dantrolene because life-threatening hyperkalemia may result. Dantrolene may aggravate previously existing muscle weakness.
- Begin cooling measures. If the individual is hyperthermic, administer iced solutions, ice packs to groin, axilla, and neck, nasogastric lavage with iced solution, or more aggressive measures as needed. Monitor body temperature every 30 minutes. Stop cooling measures at core body temperature of 38.5° C.
- Treat cardiac arrhythmias as needed. Do not use calcium channel blockers.
- Obtain blood gases, serum concentration of electrolytes and CK, blood and urine for myoglobin, and coagulation profile (INR, PTT, D-dimer) every six to 12 hours. The earliest sign of rhabdomyolysis is

myoglobinuria/myoglobinemia. Serum CK levels may not rise for several hours. Serum CK concentration may remain elevated for days and should be monitored until it returns to normal.

- Treat hyperkalemia with hyperventilation, glucose and insulin, and calcium as dictated by laboratory and cardiovascular changes.
- Ensure urine output of 2.0 mL/kg/hr with mannitol, furosemide, and fluids as needed.
- Evaluate need for invasive monitoring and continued mechanical ventilation.
- Observe the individual in an ICU for at least 36 hours because of the 25% chance of recrudescence following initial treatment. Dantrolene should be continued for at least 36 hours following successful treatment in a dose of about 1.0 mg/kg every six hours or more depending on whether signs of MH are present.
- Affected individuals who display extreme hyperthermia are at risk for disseminated intravascular coagulation. A coagulation profile (INR, PTT, D-dimer) should be obtained on all individuals experiencing fulminant MH.
- Refer the affected individual to the Malignant Hyperthermia Association of the US (MHAUS) for information and counseling. Complete the Adverse Metabolic Reaction to Anesthesia form for enrollment in the North American MH Registry.
- Refer the individual to a MH diagnostic center for muscle biopsy and contracture testing after discussion with MH consultants associated with MHAUS.

Myoglobinuria. The presence of myoglobinuria mandates referral to a neurologist for further investigation.

Prevention of Primary Manifestations

Preventive measures for individuals known to be susceptible to MH:

- For any individual undergoing anesthesia, obtain a thorough anesthetic history to determine the possibility of the individual or a family member having experienced an MH episode. When suspicion of MHS exists, family members should not be given trigger anesthetic agents (i.e., potent volatile anesthetic agents such as halothane, sevoflurane, desflurane, enflurane, and isoflurane or the depolarizing agent succinylcholine).
- In general, individuals undergoing general anesthetics that exceed 30 minutes in duration should have their temperature monitored using an electronic temperature probe. Skin liquid crystal temperature sensors are not recommended as they have been found to be unreliable indicators of changing temperature during MH events.
- Individuals with any form of myotonia (see Differential Diagnosis) should not receive succinylcholine.
- Individuals with central core disease (OMIM 117000), multiminicore disease (OMIM 255320), nemaline myopathy, congenital fiber-type disproportion, or [Duchenne or Becker muscular dystrophy](#) should not receive trigger anesthetics.
- Individuals with MHS should carry proper identification as to their susceptibility; identification bracelets are available through the [Medic Alert Foundation](#).

Agents/Circumstances to Avoid

Individuals who are MH susceptible should avoid potent inhalation anesthetics and succinylcholine.

Calcium channel blockers should not be given together with dantrolene because life-threatening hyperkalemia may result.

Serotonin antagonist (5HT₃-antagonist) antiemetics should be used cautiously, as sudden death has been reported in a child with multiminicore disease caused by a pathogenic variant in *RYR1* (p.Arg3983His) after receiving a therapeutic dose of ondansetron [Gener et al 2010].

Effective May 2008

MH Hotline
1-800-644-9737

Outside the US:
1-315-464-7079

EMERGENCY THERAPY FOR

MALIGNANT HYPERTHERMIA

DIAGNOSIS vs. ASSOCIATED PROBLEMS

Signs of MH:

- Increasing ETCO₂
- Trunk or total body rigidity
- Masseter spasm or trismus
- Tachycardia/tachypnea
- Mixed Respiratory and Metabolic Acidosis
- Increased temperature (may be late sign)
- Myoglobinuria

Sudden/Unexpected Cardiac

Arrest in Young Patients:

- Presume hyperkalemia and initiate treatment (see #6)
- Measure CK, myoglobin, ABGs, until normalized
- Consider dantrolene
- Usually secondary to occult myopathy (e.g., muscular dystrophy)
- Resuscitation may be difficult and prolonged

Trismus or Masseter Spasm with Succinylcholine

- Early sign of MH in many patients
- If limb muscle rigidity, begin treatment with dantrolene
- For emergent procedures, continue with non-triggering agents, evaluate and monitor the patient, and consider dantrolene treatment
- Follow CK and urine myoglobin for 36 hours.
- Check CK immediately and at 6 hour intervals until returning to normal. Observe for dark or cola colored urine. If present, liberalize fluid intake and test for myoglobin
- Observe in PACU or ICU for at least 12 hours

ACUTE PHASE TREATMENT

1 GET HELP. GET DANTROLENE – Notify Surgeon

- Discontinue volatile agents and succinylcholine.
- Hyperventilate with 100% oxygen at flows of 10 L/min. or more.
- Halt the procedure as soon as possible; if emergent, continue with non-triggering anesthetic technique.
- Don't waste time changing the circle system and CO₂ absorbant.

2 Dantrolene 2.5 mg/kg rapidly IV, if possible

To convert kg to lbs for amount of dantrolene, give patients 1 mg/lb (2.5 mg/kg approximates 1 mg/lb).

- Dissolve the 20 mg in each vial with at least 60 ml sterile, preservative-free water for injection. Prewarming (not to exceed 39° C.) the sterile water may expedite solubilization of dantrolene. However, to date, there is no evidence that such warming improves clinical outcome.
- Repeat until signs of MH are reversed.
- Sometimes more than 10 mg/kg (up to 30 mg/kg) is necessary.

- Each 20 mg bottle has 3 gm mannitol for isotonicity. The pH of the solution is 9.

3 Bicarbonate for metabolic acidosis

- 1-2 mEq/kg if blood gas values are not yet available.

- 4 Cool the patient with core temperature >39°C. Lavage open body cavities, stomach, bladder, or rectum. Apply ice to surface. Infuse cold saline intravenously. Stop cooling if temp. <38°C and falling to prevent drift <36°C.

5 Dysrhythmias usually respond to treatment of acidosis and hyperkalemia.

- Use standard drug therapy except calcium channel blockers, which may cause hyperkalemia or cardiac arrest in the presence of dantrolene.

6 Hyperkalemia – Treat with hyperventilation, bicarbonate, glucose/insulin, calcium.

- Bicarbonate 1-2 mEq/kg IV.
- For **pediatric**, 0.1 units insulin/kg and 1 ml/kg 50% glucose or for **adult**, 10 units regular insulin IV and 50 ml 50% glucose.
- Calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia.
- Check glucose levels hourly.

7 Follow ETCO₂, electrolytes, blood gases, CK, core temperature, urine output and color, coagulation studies. If CK and/or K⁺ rise more than transiently or urine output falls to less than 0.5 ml/kg/hr, induce diuresis to >1 ml/kg/hr and give bicarbonate to alkalinize urine to prevent myoglobinuria-induced renal failure. (See D below)

- Venous blood gas (e.g., femoral vein) values may document hypermetabolism better than arterial values.
- Central venous or PA monitoring as needed and record minute ventilation.
- Place Foley catheter and monitor urine output.

POST ACUTE PHASE

- 4 Observe the patient in an ICU for at least 24 hours, due to the risk of recrudescence.

- 5 Dantrolene 1 mg/kg q 4-6 hours or 0.25 mg/kg/hr by infusion for at least 24 hours. Further doses may be indicated.

- 6 Follow vitals and labs as above (see #7)
- Frequent ABG as per clinical signs
- CK every 8-12 hours; less often as the values trend downward

- 8 Follow urine myoglobin and institute therapy to prevent myoglobin precipitation in renal tubules and the subsequent development of Acute Renal Failure. CK levels above 10,000 IU/L is a presumptive sign of rhabdomyolysis and myoglobinuria. Follow standard intensive care therapy for acute rhabdomyolysis and myoglobinuria (urine output >2 ml/kg/hr by hydration and diuretics along with alkalization of urine with Na-bicarbonate infusion with careful attention to both urine and serum pH values).

- 9 Counsel the patient and family regarding MH and further precautions; refer them to MHAUS. Fill out and send in the Adverse Metabolic Reaction to Anesthesia (AMRA) form (www.mhreg.org) and send a letter to the patient and her/his physician. Refer patient to the nearest Biopsy Center for follow-up.

Non-Emergency Information

MHAUS
PO Box 1069 (11 East State Street)
Sherburne, NY 13460-1069

Phone
1-800-966-4287
(607-674-7901)

Fax
607-674-7930

Email
info@mhaus.org

Website
www.mhaus.org



CAUTION: This protocol may not apply to all patients; alter for specific needs.

ORPO 5/06/08

Produced by the Malignant Hyperthermia Association of the United States (MHAUS). MHAUS is a non-profit organization under IRS-Code 501(c)(3). It operates solely on contributed funds. All contributions are tax deductible. For more information, go to www.mhaus.org.

Figure 2. MHAUS treatment guide for malignant hyperthermia

Copyright, The Malignant Hyperthermia Association of the United States (MHAUS)

Individuals with MH are generally advised to avoid extremes of heat but not to restrict athletic activity or lifestyle unless they have experienced overt rhabdomyolysis or heat stroke.

In individuals with MH undergoing cardiac bypass surgery, aggressive rewarming should be avoided, as it may be associated with development of clinical signs of MH [Metterlein et al 2011b].

Evaluation of Relatives at Risk

It is appropriate to clarify the status of at-risk relatives of an affected individual in order to identify those who also have an increased susceptibility to MH and thus would benefit from avoiding anesthetic agents that increase the risk for an MH episode. Evaluations include the following:

- If the MHS-causative pathogenic variant in the family is known, molecular genetic testing can be used to establish increased risk of MH in a heterozygous individual; molecular genetic testing alone cannot be used to identify family members who are not at increased risk for MH because of other possible genetic risk factors [Hopkins et al 2015].
- If the pathogenic variant in the family is not known or if an at-risk relative is found to be negative for the familial pathogenic variant, muscle contracture testing can be used to assess susceptibility to MH.

Note: Molecular genetic testing can only be used to assess inherited risk of MH if the familial variant has been established as pathogenic through variant assessment that includes functional analysis, and assessment of co-segregation.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

If a pregnant woman with MHS requires non-emergent surgery during the pregnancy, a non-triggering anesthetic (local, nerve block, epidural, spinal anesthesia, or a total intravenous general anesthetic) should be administered. Standard American Society of Anesthesiologists mandated monitoring should be used, along with core temperature monitoring. Fetal monitoring should follow standard guidelines. Dantrolene should not be administered in preparation for surgery or labor and delivery.

Continuous epidural analgesia is highly recommended for labor and delivery. If a cesarean delivery is indicated in a woman who does not have an epidural catheter in place, neuraxial (spinal, epidural, or combined spinal-epidural) anesthesia is recommended, if not otherwise contraindicated. If a general anesthetic is indicated, a total intravenous anesthetic technique should be administered, with an anesthesia machine that has been prepared for an individual with MHS.

In the case of a fetus whose father has MHS but whose mother is not known to have MHS, regional anesthesia or general anesthesia without trigger agents is recommended.

For further information regarding the management of pregnant women with MHS, see 2009 [guidelines](#) developed by the Malignant Hyperthermia Association of the United States and Hopkins et al [2015].

Therapies Under Investigations

Preliminary investigation by Lanner et al [2012] has shown that 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) prevents heat-induced sudden death in a knockout mouse model of MH. This finding is suggestive of possible effectiveness of AICAR in the prophylactic treatment of humans with enhanced susceptibility to exercise- or heat-induced sudden death associated with *RYR1* pathogenic variants.

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](#) in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Malignant hyperthermia susceptibility (MHS) is inherited in an autosomal dominant manner.

Note: Genetic counseling for myopathic disorders that predispose to classic MH is not addressed in this section (see Clinical Description).

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with MHS have a parent with MHS; the parent may not have experienced an episode of MH.
- A proband with MHS may have the disorder as the result of a *de novo* pathogenic variant. *De novo* pathogenic variants have been detected; however, the proportion of individuals with MHS caused by a *de novo* variant is unknown.
- If neither parent is known to have MHS, recommendations for evaluation of the parents include molecular genetic testing if the MHS-causative pathogenic variant has been identified in the proband and muscle contracture testing (see Evaluation of Relatives at Risk).
- The family history of some individuals diagnosed with MHS may appear to be negative because of reduced penetrance of the MHS-causative pathogenic variant or absence of a triggering event in heterozygous family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations have been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has MHS and/or is known to have an MHS-causative pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known MHS-causative pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the risk to the sibs of inheriting the pathogenic variant is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If both parents are clinically unaffected based on contracture testing, the risk to the sibs of a proband is the same as in the general population.

Offspring of a proband. Each child of an individual with MHS has a 50% chance of inheriting the MHS-causative pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has had an episode of MH and/or is known to have an MHS-causative pathogenic variant, members of the parent's family are at risk.

Specific risk issues. Risk for MH is predominantly a problem under general anesthesia with trigger anesthetics. A very small number of individuals with MH susceptibility appear to be at risk for heat stroke or exercise-induced rhabdomyolysis. MH has been reported to occur in individuals without anesthetic exposure [Tobin et al 2001, Groom et al 2011].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the MHS-causative pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **European Malignant Hyperthermia Group (EMHG)**

Dr. PM Hopkins, University Department of Anaesthesia, St James' University Trust Hospital

Beckett Street

Clinical Science Building

Leeds LS9 7TF

United Kingdom

Phone: +44 113 206 52 74

Fax: +44 113 283 69 72

Email: p.m.hopkins@leeds.ac.uk

www.emhg.org

- **Malignant Hyperthermia Association of the United States (MHAUS)**

11 East State Street

PO Box 1069

Sherburne NY 13460

Phone: 800-644-9737 (Toll-free Emergency Hotline); 607-674-7901; 315-464-7079

Fax: 607-674-7910

Email: info@mhaus.org

www.mhaus.org

- **North American Malignant Hyperthermia Registry**

The NAMHR collects, analyzes, and disseminates information on the presentation, diagnosis, treatment, and response to treatment of MH in affected individuals.

Phone: 888-274-7899 (toll-free); 352-392-7029

Email: agunnett@anest.ufl.edu

www.anest.ufl.edu/namhr

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Malignant Hyperthermia Susceptibility: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CACNA1S	1q32.1	Voltage-dependent L-type calcium channel subunit alpha-1S	Calcium channel, voltage-dependent, L type, alpha 1S subunit (CACNA1S) @ LOVD	CACNA1S	CACNA1S
RYR1	19q13.2	Ryanodine receptor 1	Leiden Muscular Dystrophy pages (RYR1)	RYR1	RYR1
STAC3	12q13.3	SH3 and cysteine-rich domain-containing protein 3		STAC3	STAC3

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Malignant Hyperthermia Susceptibility ([View All in OMIM](#))

114208	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1S SUBUNIT; CACNA1S
145600	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 1; MHS1
154275	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 2
154276	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 3
180901	RYANODINE RECEPTOR 1; RYR1
600467	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 4
601887	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 5; MHS5
601888	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 6
615521	SH3 AND CYSTEINE-RICH DOMAINS 3; STAC3

Molecular Pathogenesis

Intracellular calcium is controlled through a storage site within the muscle called the sarcoplasmic reticulum. A channel called the ryanodine receptor type 1 (RYR1), encoded by *RYR1*, controls the release of calcium from the sarcoplasmic reticulum. In MHS, pathogenic variants in *RYR1* cause the RYR1 channel to become leaky, leading to an uncontrolled rise in calcium levels within the muscle cell. When this happens, muscle contraction is activated, metabolism increases in order to sustain the contraction, and heat results from the metabolic processes.

Uncontrolled muscle contraction also increases production of acid in the muscle as a result of depletion of energy stores. The cell membrane permeability decreases leading to potassium leakage, which may lead to fatal arrhythmias and creatine kinase leakage into the circulation.

Dantrolene sodium reverses the leak of calcium from the sarcoplasmic reticulum and stops the process.

Mechanism of disease causation. Gain of function

Gene-specific laboratory technical considerations. Note that because of the gain-of-function disease mechanism, genetic heterogeneity, and variable expressivity of this disorder, data from functional studies are critical in reaching a likely pathogenic or pathogenic classification using ACMG criteria.

Functional consequence of *RYR1* variants on RYR1 function can be analyzed by one or more of the following test systems using recombinant in vitro expression on a defined genetic background:

- Measurement of calcium release in response to trigger agents in HEK293 cells [Tong et al 1997, Sambuughin et al 2001b]
- Measurement of calcium release in response to trigger agents in myotubes of the dyspedic mouse (*RYR1*-knockout) transfected with a rabbit *RYR1* cDNA construct-containing variant being tested [Yang et al 2003].

In addition, the diagnosis of MHS can be established by calcium measurements and ligand binding studies of the following in affected individuals:

- Myotubes [Brinkmeier et al 1999];
- Microsomal sarcoplasmic reticulum preparations from muscle biopsy [Richter et al 1997];
- Microsomal sarcoplasmic reticulum preparations from lymphoblasts [Tilgen et al 2001].

All assays should be performed on samples from at least two independent affected individuals with the same variant.

Table 7. Malignant Hyperthermia Susceptibility: Gene-Specific Laboratory Technical Considerations

Gene ¹	Considerations
<i>CACNA1S</i>	None
<i>RYR1</i>	Exon 91 is highly GC rich.
<i>STAC3</i>	None

1. Genes from Table 3 in alphabetic order

Chapter Notes

Acknowledgments

Supported by grants from the National Institutes of Health (AR044657, AR053349 and AR052354 to RTD).

Author History

Robert T Dirksen, PhD (2006-present)

Sheila Riazi, MD (2013-present)

Henry Rosenberg, MD (2003-present)

Nyamkhishig Sambuughin, PhD (2003-2006; 2010-present)

Revision History

- 16 January 2020 (sw) Comprehensive update posted live
- 31 January 2013 (me) Comprehensive update posted live
- 19 January 2010 (me) Comprehensive update posted live
- 12 May 2006 (me) Comprehensive update posted live
- 19 December 2003 (me) Review posted live
- 19 June 2003 (hr) Original submission

References

Published Guidelines / Consensus Statements

North American Guidelines for Testing

Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA*. 2005;293:2918–24. PubMed PMID: 15956637.

Riazi S, Kraeva N, Hopkins PM. Updated guide for the management of malignant hyperthermia. *Can J Anaesth*. 2018;65:709–21. PubMed PMID: 29600483.

See also guidelines on mhaus.org.

European Guidelines for Testing

Glahn KP, Ellis FR, Halsall PJ, Müller CR, Snoeck MM, Urwyler A, Wappler F; European Malignant Hyperthermia Group. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth*. 2010;105:417–20. PubMed PMID: 20837722.

Hopkins PM, Gupta PK, Bilmen JG. Malignant hyperthermia. *Handb Clin Neurol*. 2018;157:645–61. PubMed PMID: 30459030.

Hopkins PM, Rüffert H, Snoeck MM, Girard T, Glahn KP, Ellis FR, Müller CR, Urwyler A, et al. OUP guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth*. 2015;115:531–9. PubMed PMID: 26188342.

Guidelines on Diagnosis, Management, and Transfer of Care from Ambulatory Surgery Centers

Larach MG, Dirksen SJ, Belani KG, Brandom BW, Metz KM, Policastro MA, Rosenberg H, Valedon A, Watson CB. Creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. Available [online](#). 2012. Accessed 6-1-22.

Riazi S, Kraeva N, Hopkins PM. Updated guide for the management of malignant hyperthermia. *Can J Anaesth*. 2018;65:709–21. PubMed PMID: 29600483.

North American Recommendations

Adverse effects of heat and exercise in relation to MH susceptibility. Available [online](#). Accessed 6-1-22.

MH susceptibility and operating room personnel. Available [online](#). Accessed 6-1-22.

Mitochondrial myopathies and malignant hyperthermia susceptibility. Available [online](#). Accessed 6-1-22.

Parturient with MHS partner. Available [online](#). Accessed 6-1-22.

Preparation of anesthesia workstations to anesthetize MH-susceptible patients. Available [online](#). Accessed 6-1-22.

Temperature monitoring during surgical procedures. Available [online](#). Accessed 6-1-22.

Literature Cited

Allen GC, Larach MG, Kunselman AR. The sensitivity and specificity of the caffeine-halothane contracture test: a report from the North American Malignant Hyperthermia Registry. The North American Malignant Hyperthermia Registry of MHAUS. *Anesthesiology*. 1998;88:579–88. PubMed PMID: 9523799.

Betzenhauser MJ, Marks AR. Ryanodine receptor channelopathies. *Pflugers Arch*. 2010;460:467–80. PubMed PMID: 20179962.

Brady JE, Sun LS, Rosenberg H, LiG. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001–2005. *Anesth Analg*. 2009;109:1162–6. PubMed PMID: 19762744.

Brandom BW, Larach MG, Chen MS, Young MC. Complications associated with the administration of dantrolene 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. *Anesth Analg*. 2011;112:1115–23. PubMed PMID: 21372281.

Brandom BW, Muldoon SM. Estimation of the incidence of malignant hyperthermia using a capture-recapture method in the USA. Abstract A1267. Las Vegas, NV: American Society of Anesthesiologists Annual Meeting. 2004.

Brinkmeier H, Kramer J, Kramer R, et al. Malignant hyperthermia causing Gly2435Arg mutation of the ryanodine receptor facilitates ryanodine-induced calcium release in myotubes. *Br J Anaesth*. 1999;83:855–61. PubMed PMID: 10700782.

Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg*. 2009;109:1065–9. PubMed PMID: 19617585.

Carpenter D, Robinson RL, Qunnel RJ, Ringrose C, Hogg M, Cason F, Booms P, Iles DE, Halsall PJ, Steele DS, Shaw MA, Hopkins PM. Genetic variation in RYR1 and malignant hyperthermia phenotypes. *Br J Anaesth*. 2009;103:538–48. PubMed PMID: 19648156.

Chelu MG, Goonasekera SA, Durham WJ, Tang W, Lueck JD, Riehl J, Pessah IN, Zhang P, Bhattacharjee MB, Dirksen RT, Hamilton SL. Heat- and anesthesia-induced malignant hyperthermia in an RyR1 knock-in mouse. *FASEB J*. 2006;20:329–30. PubMed PMID: 16284304.

Davis M, Brown R, Dickson A, Horton H, James D, Laing N, Marston R, Norgate M, Perlman D, Pollock N, Stowell K. Malignant hyperthermia associated with exercise-induced rhabdomyolysis or congenital abnormalities and a novel RYR1 mutation in New Zealand and Australian pedigrees. *Br J Anaesth*. 2002;88:508–15. PubMed PMID: 12066726.

- Duke AM, Hopkins PM, Calaghan SC, Halsall JP, Steele DS. Store-operated Ca²⁺ entry in malignant hyperthermia-susceptible human skeletal muscle. *J Biol Chem*. 2010;285:25645–53. PubMed PMID: 20566647.
- Durham WJ, Aracena-Parks P, Long C, Rossi AE, Goonasekera SA, Boncompagni S, Gilman CP, Galvan DL, Baker M, Shirokova N, Protasi P, Dirksen RT, Hamilton S. RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knock-in mice. *Cell*. 2008;133:53–65. PubMed PMID: 18394989.
- Galli L, Orrico A, Lorenzini S, Censini S, Falciani M, Covacci A, Tegassini V, Sorrentino V. Frequency and localization of mutations in the 106 exons of the RYR1 gene in 50 individuals with malignant hyperthermia. *Hum Mutat*. 2006;27:830. PubMed PMID: 16835904.
- Gener B, Burns JM, Griffin S, Boyer EW. Administration of ondansetron is associated with lethal outcome. *Pediatrics*. 2010;125:e1514–7. PubMed PMID: 20439600.
- Gonsalves SG, Ng D, Johnston JJ, Teer JK, Stenson PD, Cooper DN, Mullikin JC, Biesecker LG, et al. Using exome data to identify malignant hyperthermia susceptibility mutations. *Anesthesiology*. 2013;119:1043–53. PubMed PMID: 24195946.
- Groom L, Muldoon SM, Tang ZZ, Brandom BW, Bayarsaikhan M, Bina S, Lee HS, Qiu X, Sambuughin N, Dirksen RT. Identical de novo mutation in the type 1 ryanodine receptor gene associated with fatal, stress-induced malignant hyperthermia in two unrelated families. *Anesthesiology*. 2011;115:938–45. PubMed PMID: 21918424.
- Hayes J, Veyckemans F, Bissonnette B. Duchenne muscular dystrophy: an old anesthesia problem revisited. *Paediatr Anaesth*. 2008;18:100–6. PubMed PMID: 18184239.
- Hopkins PM, Gupta PK, Bilmen JG. Malignant hyperthermia. *Handb Clin Neurol*. 2018;157:645–61. PubMed PMID: 30459030.
- Hopkins PM, Rüffert H, Snoeck MM, Girard T, Glahn KP, Ellis FR, Müller CR, Urwyler A, et al. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth*. 2015;115:531–9. PubMed PMID: 26188342.
- Horstick EJ, Linsley JW, Dowling JJ, Hauser MA, McDonald KK, Ashley-Koch A, Saint-Amant L, Satish A, Cui WW, Zhou W, Sprague SM, Stamm DS, Powell CM, Speer MC, Franzini-Armstrong C, Hirata H, Kuwada JY. Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. *Nat Commun*. 2013;4:1952. PubMed PMID: 23736855.
- Ibarra Moreno CA, Hu S, Kraeva N, Schuster F, Johannsen S, Rueffert H, Klingler W, Heytens L, Riazi S. An assessment of penetrance and clinical expression of malignant hyperthermia in individuals carrying diagnostic RYR1 mutations. *Anesthesiology*. 2019;131:983–91. PubMed PMID: 31206373.
- Jurkat-Rott K, McCarthy T, Lehmann-Horn F. Genetics and pathogenesis of malignant hyperthermia. *Muscle Nerve*. 2000;23:4–17. PubMed PMID: 10590402.
- Karan SM, Crowl F, Muldoon SM. Malignant hyperthermia masked by capnographic monitoring. *Anesth Analg*. 1994;78:590–2. PubMed PMID: 8109781.
- Kraeva N, Riazi S, Loke J, Frodis W, Crossan ML, Nolan K, Kraev A, MacLennan DH. Ryanodine receptor type 1 gene mutations found in the Canadian malignant hyperthermia population. *Can J Anaesth*. 2011;58:504–13. PubMed PMID: 21455645.
- Kraeva N, Sapa A, Dowling JJ, Riazi S. Malignant hyperthermia susceptibility in patients with exertional rhabdomyolysis: A retrospective cohort study and updated systematic review. *Can J Anaesth*. 2017;64:736–43. PubMed PMID: 28326467.
- Lanner JT, Georgiou DK, Dagnino-Acosta A, Ainbinder A, Cheng Q, Joshi AD, Chen Z, Yarotskyy V, Oakes JM, Lee CS, Monroe TO, Santillan A, Dong K, Goodyear L, Ismailov II, Rodney GG, Dirksen RT, Hamilton SL.

- AICAR prevents heat-induced sudden death in RyR1 mutant mice independent of AMPK activation. *Nat Med*. 2012;18:244–51. PubMed PMID: 22231556.
- Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. *Anesthesiology*. 2008;108:603–11. PubMed PMID: 18362591.
- Larach MG, Dirksen SJ, Belani KG, Brandom BW, Metz KM, Policastro MA, Rosenberg H, Valedon A, Watson CB, et al. Special article: Creation of a guide for the transfer of care of the malignant hyperthermia patient from ambulatory surgery centers to receiving hospital facilities. *Anesth Analg*. 2012;114:94–100. PubMed PMID: 22052978.
- Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg*. 2010;110:498–507. PubMed PMID: 20081135.
- Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RE, Muldoon SM, Nelson TE, Ording H, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology*. 1994;80:771–9. PubMed PMID: 8024130.
- Li G, Brady JE, Rosenberg H, Sun LS. Excess comorbidities associated with malignant hyperthermia diagnosis in pediatric hospital discharge records. *Paediatr Anaesth*. 2011;21:958–63. PubMed PMID: 21722230.
- Litman RS, Rosenberg H. Malignant hyperthermia: update on susceptibility testing. *JAMA*. 2005;293:2918–24. PubMed PMID: 15956637.
- Marchant CL, Ellis FR, Halsall PJ, Hopkins PM, Robinson RL. Mutation analysis of two patients with hypokalemic periodic paralysis and suspected malignant hyperthermia. *Muscle Nerve*. 2004;30:114–7. PubMed PMID: 15221887.
- Metterlein T, Zink W, Kranke E, Haneya A, Graf B, Kranke P. Cardiopulmonary bypass in malignant hyperthermia susceptible patients: a systematic review of published cases. *J Thorac Cardiovasc Surg*. 2011b;141:1488–95. PubMed PMID: 21376345.
- Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle. *Am J Hum Genet*. 1997;60:1316–25. PubMed PMID: 9199552.
- Mungunsukh O, Deuster P, Muldoon S, O'Connor F, Sambuughin N. Estimating prevalence of malignant hyperthermia susceptibility through population genomics data. *Br J Anaesth*. 2019;123:e461–e463. PubMed PMID: 31301762.
- Parness J, Bandschapp O, Girard T. The myotonias and susceptibility to malignant hyperthermia. *Anesth Analg*. 2009;109:1054–64. PubMed PMID: 19762732.
- Paul-Pletzer K, Yamamoto T, Bhat MB, Ma J, Ikemoto N, Jimenez LS, Morimoto H, Williams PG, Parness J. Identification of a dantrolene-binding sequence on the skeletal muscle ryanodine receptor. *J Biol Chem*. 2002;277:34918–23. PubMed PMID: 12167662.
- Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet*. 2016;48:126–33. PubMed PMID: 26656846.
- Riazi S, Kraeva N, Hopkins PM. Malignant Hyperthermia in the Post-Genomics Era: New Perspectives on an Old Concept. *Anesthesiology*. 2018;128:168–80. PubMed PMID: 28902675.
- Richter M, Schleithoff L, Deufel T, Lehmann-Horn F, Hermann-Frank A. Functional characterisation of distinct ryanodine receptor mutation in human malignant hyperthermia susceptible muscle. *J Biol Chem*. 1997;272:5256–60. PubMed PMID: 9030597.

- Robinson RL, Brooks C, Brown SL, Ellis FR, Halsall PJ, Quinnell RJ, Shaw MA, Hopkins PM. RYR1 mutations causing central core disease are associated with more severe malignant hyperthermia in vitro contracture test phenotypes. *Hum Mutat.* 2002;20:88–97. PubMed PMID: 12124989.
- Robinson R, Carpenter D, Shaw M-A, Halsall J, Hopkins P. Mutations in RYR1 in malignant hyperthermia and central core disease. *Hum Mutat.* 2006;27:977–89. PubMed PMID: 16917943.
- Robinson RL, Anetseder MJ, Brancadoro V, Van Broekhoven C, Carsana A, Censier K, Fortunato G, Girard T, Heytens L, Hopkins PM, Jurkat-Rott K, Klinger W, Kozak-Ribbens G, Krivosic R, Monnier N, Nivoche Y, Olthoff D, Rueffert H, Sorrentino V, Tegazzin V, Mueller CR. Recent advances in the diagnosis of malignant hyperthermia susceptibility: How confident can we be of genetic testing? *Eur J Hum Genet.* 2003;11:342–8. PubMed PMID: 12700608.
- Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: A review. *Orphanet J Rare Dis.* 2015;10:93. PubMed PMID: 26238698.
- Rosero EB, Adesanya AL, Timarra CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States 2000–2005. *Anesthesiology.* 2009;110:89–94. PubMed PMID: 19104175.
- Sambuughin N, Capacchione J, Blokhin A, Bayarsaikhan M, Bina S, Muldoon S. The ryanodine receptor type 1 gene variants in African American men with exertional rhabdomyolysis and malignant hyperthermia susceptibility. *Clin Genet.* 2009;76:564–8. PubMed PMID: 19807743.
- Sambuughin N, Holley H, Muldoon S, Brandom BW, de Bantel AM, Tobin JR, Nelson TE, Goldfarb LG. Screening of the entire ryanodine receptor type 1 coding region for sequence variants associated with malignant hyperthermia susceptibility in the north american population. *Anesthesiology.* 2005;102:515–21. PubMed PMID: 15731587.
- Sambuughin N, McWilliams S, de Bantel A, Sivakumar K, Nelson TE. Single-amino-acid deletion in the RYR1 gene, associated with malignant hyperthermia susceptibility and unusual contraction phenotype. *Am J Hum Genet.* 2001a;69:204–8. PubMed PMID: 11389482.
- Sambuughin N, Nelson TE, Jankovic J, Xin C, Meissner G, Mullakandov M, Ji J, Rosenberg H, Sivakumar K, Goldfarb LG. Identification and functional characterization of a novel ryanodine receptor mutation causing malignant hyperthermia in North American and South American families. *Neuromuscul Disord.* 2001b;11:530–7. PubMed PMID: 11525881.
- Sato T, Nishio H, Iwata M, Kentotsuboi, Tamura A, Miyazaki T, Suzuki K. Postmortem molecular screening for mutations in ryanodine receptor type 1 (RYR1) gene in psychiatric patients suspected of having died of neuroleptic malignant syndrome. *Forensic Sci Int.* 2010;194:77–9. PubMed PMID: 19931341.
- Stewart SL, Hogan K, Rosenberg H, Fletcher JE. Identification of the Arg1086His mutation in the alpha subunit of the voltage-dependent calcium channel (CACNA1S) in a North American family with malignant hyperthermia. *Clin Genet.* 2001;59:178–84. PubMed PMID: 11260227.
- Tilgen N, Zorzato F, Halliger-Keller B, et al. Identification of four novel mutations in the C-terminal membrane spanning domain of the ryanodine receptor 1: association with central core disease and alteration of calcium homeostasis. *Hum Mol Genet.* 2001;10:2879–87. PubMed PMID: 11741831.
- Tobin JR, Jason DR, Challa VR, Nelson TE, Sambuughin N. Malignant hyperthermia and apparent heat stroke. *JAMA.* 2001;286:168–9. PubMed PMID: 11448278.
- Tong J, Oyamada H, Demareux N, Grinstein S, McCarthy TV, MacLennan DH. Caffeine and Halothane sensitivity of intracellular Ca²⁺ release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease. *J Biol Chem.* 1997;272:26332–9. PubMed PMID: 9334205.

- Turan A, Mendoza ML, Gupta S, You J, Gottlieb A, Chu W, Saager L, Sessler DI. Consequences of succinylcholine administration to patients using statins. *Anesthesiology*. 2011;115:28–35. PubMed PMID: 21606827.
- Vladutiu GD, Isackson PJ, Kaufman K, Harley JB, Cobb B, Christopher-Stine L, Wortmann RL. Genetic risk for malignant hyperthermia in non-anesthesia-induced myopathies. *Mol Genet Metab*. 2011;104:167–73. PubMed PMID: 21795085.
- Wappler F, Fiege M, Steinfath M, Agarwal K, Scholz J, Singh S, Matschke J, Schulte Am Esch J. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology*. 2001;94:95–100. PubMed PMID: 11135728.
- Yang T, Allen PD, Pessah IN, Lopez JR. Enhanced excitation-coupled calcium entry in myotubes is associated with expression of RyR1 malignant hyperthermia mutations. *J Biol Chem*. 2007;282:37471–8. PubMed PMID: 17942409.
- Yang T, Riehl J, Esteve E, Matthaei KI, Goth S, Allen PD, Pessah IN, Lopez JR. Pharmacologic and functional characterization of malignant hyperthermia in the R163C RyR1 knock-in mouse. *Anesthesiology*. 2006;105:1164–75. PubMed PMID: 17122579.
- Yang T, Ta TA, Pessah IN, Allen PD. Functional defects in six ryanodine receptor isoform-1 (RyR1) mutations associated with malignant hyperthermia and their impact on skeletal excitation-contraction coupling. *J Biol Chem*. 2003;278:25722–30. PubMed PMID: 12732639.
- Zaharieva IT, Sarkozy A, Munot P, Manzur A, O'Grady G, Rendu J, Malfatti E, Amthor H, Servais L, Urtizberea JA, Neto OA, Zanuteli E, Donkervoort S, Taylor J, Dixon J, Poke G, Foley AR, Holmes C, Williams G, Holder M, Yum S, Medne L, Quijano-Roy S, Romero NB, Fauré J, Feng L, Bastaki L, Davis MR, Phadke R, Sewry CA, Bönnemann CG, Jungbluth H, Bachmann C, Treves S, Muntoni F. STAC3 variants cause a congenital myopathy with distinctive dysmorphic features and malignant hyperthermia susceptibility. *Hum Mutat*. 2018;39:1980–94. PubMed PMID: 30168660.

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.