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Malignant Hyperthermia Susceptibility

Synonym: Malignant Hyperpyrexia

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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 release calcium stores from the sarcoplasmic reticulum and may promote entry of calcium from 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 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 affected individuals 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. A clinical grading scale helps determine if a malignant hyperthermia (MH) episode has occurred. Contracture testing, the standard diagnostic test for MH since the mid-1970s, relies on the in vitro measurement of contracture response of biopsied muscle to graded concentrations of caffeine, the anesthetic halothane, and other calcium-releasing agents. To date, two genes predisposing to MHS have been identified; four additional loci have been mapped, but the genes have not been identified. MHS1 is associated with mutation of *RYR1,* encoding ryanodine receptor type 1; MHS5 is associated with mutation of *CACNA1S,* encoding a skeletal muscle calcium channel. Up to 70% of MHS is caused by mutation of *RYR1* and about 1% results from mutation of *CACNA1S*.

Management. *Treatment of manifestations:* Early diagnosis of MHS is essential. Successful treatment of an acute episode of MH includes:

- Discontinuation of potent inhalation agents and succinylcholine;
- Administration of dantrolene sodium intravenously;
- Surface, intravenous and body cavity cooling with cold solutions for hyperthermic

individuals; and

- Treatment of metabolic abnormalities.

Affected individuals who display extreme hyperthermia are at risk for disseminated intravascular coagulation; therefore, a coagulation profile should be obtained on all individuals experiencing fulminant MH. The presence of myoglobinuria mandates referral to a neurologist for further investigation.

Prevention of primary manifestations: Avoidance of potent volatile anesthetic agents and succinylcholine. Individuals undergoing general anesthetics that exceed 30 minutes in duration should have their temperature monitored using an electronic temperature probe.

Agents/circumstances to avoid: Avoid extremes of heat, but do not restrict athletic activity unless there is a history of overt rhabdomyolysis and/or heat stroke. Calcium channel blockers should not be given together with dantrolene because life-threatening hyperkalemia may result. 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. Serotonin antagonist antiemetics should be used cautiously.

Evaluation of relatives at risk: If the pathogenic variant has been identified in the family, molecular genetic testing of at-risk relatives is warranted to identify those who have the pathogenic variant and will benefit from avoiding anesthetic agents that increase the risk for a malignant hyperthermia episode. Absence of a pathogenic variant does not imply that an at-risk individual is not MH susceptible.

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. 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 inherited in an autosomal dominant manner. Most individuals diagnosed with MHS have a parent with MHS; however, 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 the pathogenic variant. Although prenatal diagnosis for pregnancies at increased risk for MHS is possible, prenatal testing for pharmacogenetic conditions (like MHS) that have effective treatment and prevention is generally not offered or available.

Diagnosis

Clinical Diagnosis

Consensus guidelines for the diagnosis and management of malignant hyperthermia have been published [Robinson & Hopkins 2001, Urwyler et al 2001, Sei et al 2004, Litman & Rosenberg

2005, Carpenter et al 2009, Glahn et al 2010]. Clinical diagnostic criteria for malignant hyperthermia susceptibility (MHS) are 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 malignant hyperthermia as determined through a Delphic study of experts. Points are assigned according to weight and are then summed to produce a raw score, which translates to a likelihood score, range from 1 (score 0: "almost never/very unlikely") to 6 (score ≥50: "almost certain"). The more criteria an individual fulfills, the more likely that a malignant hyperthermia (MH) episode has occurred. Thus, with only temperature elevation during anesthesia, an individual is not likely to be susceptible to malignant hyperthermia. Of course, a limitation of the scoring system is that not every clinical finding may be measured, e.g. arterial blood gas, or the syndrome is recognized very quickly and treated before all signs appear [Larach et al 1994].

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 mmHg, $PaCO_2$ >60 mmHg
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 [2002]

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

Testing

Contracture test. Since the mid-1970s, the standard diagnostic test for MH 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:

Note: The calcium-induced calcium release (CICR) 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 a MH diagnostic center (see Testing Strategy, *Note) in order to undergo testing.
- The individual is anesthetized with general anesthesia 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 buffer solution and, after a period of stabilization, are caused to contract with supramaximal electrical stimuli. The isometric contracture that develops following exposure to various pharmacologic agents that cause sarcoplasmic reticulum (SR) 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 [Urwyler et al 2001]. 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). Of note, in recent years, ryanodine (1.0 µmol/L) and 4-chloro-m-cresol have been used to elicit contractures as well.

Table 2.

Testing Protocols for Malignant Hyperthermia

Designation [1]	North American Protocol	European Protocol
MHS	Contracture of >0.7 g to 3% halothane OR Contracture of >0.3 g to 2.0 mmol/L caffeine	Contracture of ≥0.2 g to ≤2% halothane AND Contracture of ≥0.2 g to ≤2.0 mmol/L caffeine
MHE [2]	Contracture of 0.5-0.7 g to 3% halothane	Contracture to halothane only or caffeine only
	No contracture OR Contracture of <0.5 g to halothane	No significant contractures to either

MHN	OR Contracture of <0.3 g to 2.0 mmol/L caffeine	agent

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 µmol/L ryanodine or 4-chloro-m-chlorocresol in addition to halothane and caffeine to clarify equivocal results; however, these agents have not been incorporated into the standardized test.

1. MHS = malignant hyperthermia susceptible; MHE = malignant hyperthermia equivocal; MHN = malignant hyperthermia negative
2. In the North American protocol, the MHE designation is "optional"; and most centers report results as either MHN or MHS using a threshold of 0.5 g.

Sevoflurane has been investigated as a potential replacement for halothane in the MH testing protocol. Preliminary results suggest the rapid application of sevoflurane (8%), and not its incremental increase, induces significant contracture in MHS, and may differentiate MHS from MHN [Metterlein et al 2011a].

Molecular Genetic Testing

Genes. To date, only two genes in which mutation causes MHS have been identified:

- ***RYR 1*** **(MHS1 locus)** encodes the type 1 ryanodine receptor of skeletal muscle. Molecular genetic testing indicates that pathogenic variants in *RYR1* are identified in up to 70%-80% of individuals with confirmed MHS [Sambuughin et al 2005, Galli et al 2006, Robinson et al 2006, Kraeva et al 2011].
- ***CACNA1S*** **(MHS5 locus)** encodes the α_1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel. Pathogenic variants in *CACNA1S* account for 1% of all MHS [Stewart et al 2001].

Evidence for further locus heterogeneity. Four additional loci have been mapped; the genes have not been identified:

- **MHS2** (linked to chromosome locus 17q11.2-q24)
- **MHS4** (3q13)
- MHS6 (5p)
- **MHS3** (7q21-q22)

Clinical testing

Table 3.

Summary of Molecular Genetic Testing Used in Malignant Hyperthermia Susceptibility

Gene [1]	Proportion of MHS		Variants

Locus	Attributed to Mutation of This Gene	Test Method	Detected [2]
RYR1 / MHS1	70%-80%	Targeted analysis for pathogenic variants	Pathogenic variant panel [3]
		Sequence analysis [4] / scanning of all exons and flanking intronic regions [5, 6]	Sequence variants
		Sequence analysis [4] / scanning of select exons & flanking intronic regions [5, 6]	Sequence variants
	Unknown	Deletion/duplication analysis	Unknown; none reported
	Unknown	Linkage analysis [7]	NA
CACNA1S / MHS5	1% [8]	Targeted analysis for pathogenic variants	p.Arg1086His
		Sequence analysis [4] / variant scanning [5]	Sequence variants
		Sequence analysis of select exons	Sequence variants [9]
	Unknown	Linkage analysis [7]	NA
Unknown / MHS2	Unknown	Linkage analysis [7]	NA
Unknown / MHS3	Unknown	Linkage analysis [7]	NA
Unknown / MHS4	Unknown	Linkage analysis [7]	NA

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. Examples of variants detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.
4. A panel of the most common pathogenic variants (Table 4) detects approximately 25%-30% of individuals with malignant hyperthermia susceptibility (MHS) [Robinson et al 2002]. In some populations, (i.e., in Switzerland) a more limited panel is acceptable because of homogeneity of the population [Girard et al 2001]. Pathogenic variant panel is p.Cys35Arg, p.Arg163Cys, p.Arg163Leu, p.Gly248Arg, p.Gly341Arg p.Ile403Met, p.Tyr522Ser, p.Arg552Trp, p.Arg614Cys, p.Arg614Leu, p.Arg2163His, p.Arg2163Cys, p.Val2168Met, p.Thr2206Met, p.Ala2350Thr, p.Ala2428Thr, p.Gly2434Arg, p.Arg2435His, p.Arg2454Cys, p.Arg2454His, p.Arg2458His, p.Arg2458Cys, p.Gly341Arg, and p.Tyr522Ser (see Table 4). Pathogenic variant panels may vary by laboratory.

5. Sequence analysis and variant scanning of the entire gene can have similar variant detection frequencies; however, variant detection rates for variant scanning may vary considerably between laboratories depending on the specific protocol used.
6. Although many *RYR1* pathogenic variants are clustered in three mutational hot spots, ranging from amino acid residues 35 to 614 (N-terminal region), 2117 to 2458 (central region), and 3916 to 4973 (C-terminal region) [Jurkat-Rott et al 2000, McCarthy et al 2000, Robinson et al 2006], pathogenic variants are found throughout the *RYR1* coding region [Kraeva et al 2011]. When individuals who have either a positive contracture test or strongly suggestive clinical and family histories are selected, complete sequence analysis of the entire *RYR1* coding region increases the detection rate to 70%-80% [Sambuughin et al 2005, Galli et al 2006].
7. Linkage analysis for all MHS loci may be considered for genetic counseling in families in which at least ten family members in more than two generations have the unequivocal diagnosis of MHS by IVCT. Linkage studies are always based on accurate clinical diagnosis of MHS in the affected family members and accurate understanding of the genetic relationships in the family. In addition, linkage analysis depends on the availability and willingness of family members to be tested and on the presence of informative polymorphic markers.
8. Exact frequency is unknown because of the small number of individuals with MHS attributed to mutation of this gene.
9. Exons sequenced may vary by laboratory.

Interpretation of test results

- Failure to detect a pathogenic variant on molecular genetic testing does **not** rule out MH susceptibility.
- Discordance between the contracture test and molecular genetic test results is observed in up to 10% of individuals.

Test characteristics. See Clinical Utility Gene Card [Rosenberg & Rueffert 2011] for information on test characteristics including sensitivity and specificity.

Testing Strategy

Indications for muscle biopsy and contracture testing to confirm the diagnosis in a proband (see *Note)

Definite indications

- Proband with a 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
- 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 suspicion of MHS 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 should undergo biopsy, following careful discussion of the pros and cons of the test:

- Isolated masseter muscle rigidity with succinylcholine
- 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
- Signs suggestive of but not definitive for MH

Not recommended

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

*Note: (1) Because the test is available on a limited basis, some physicians consider all individuals with a history suspicious for 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 his/her family. (2) Details regarding MH muscle biopsy centers can be obtained from the Malignant Hyperthermia Association of the US Web site (www.mhaus.org).

Indications for molecular genetic testing (see **Note)

- Confirmed clinical episode of MH
- Positive halothane/caffeine contracture test
- High likelihood of having experienced a 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 in the absence of a known myopathy

**Note: Recommendations pertain to North America. The European MH group does not perform molecular genetic testing unless an individual or his/her relative has had a positive contracture test.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of

the pathogenic variant in the family.

Clinical Characteristics

Clinical Description

Malignant hyperthermia susceptibility. The manifestations of 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. At first, MH was thought, in all cases, to consist of an extremely elevated body temperature, skeletal muscle rigidity, and acidosis associated with a high mortality rate. However, it is now recognized that MH is an inherited pharmacogenetic disorder of calcium regulation resulting in uncontrolled skeletal muscle hypermetabolism [Hopkins 2000] with varied presentations, depending on the triggering agents and environmental factors, such as metabolic state and body temperature, at the beginning of anesthesia.

The triggering substances release calcium stores from the sarcoplasmic reticulum via the muscle ryanodine receptor, the calcium release channel leading to an increase in the concentration of free myoplasmic calcium. There is also evidence that store operated calcium (calcium contained in the extracellular fluid) entry also plays a role in the pathophysiology of MH [Duke et al 2010]. Increased myoplasmic calcium causes contracture of skeletal muscles and activates glycogenolysis and cell metabolism, resulting in production of heat and excess lactate. Activation of the oxidative cycle leads to high oxygen consumption and high carbon dioxide.

The clinical manifestations are somewhat variable depending on the clinician's response. Hypercapnia is common, as is tachycardia. Hyperthermia follows and may be an early sign of MH. However, failure to monitor core temperature may lead to a delay in detecting hyperthermia. Skin temperature is often misleading in 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 cases, for reasons that are not clear. In some cases 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].

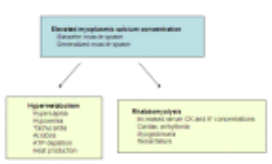

Figure 1.

Clinical features of malignant hyperthermia susceptibility
Note: Early diagnosis and rapid therapy are both life-saving and lead to a reduction of the clinical symptoms. Adapted from Jurkat-Rott et al [2000]

MH may appear at any point during anesthetization or within an hour or so of the 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 cases, the first manifestations of MH occur in the operating room. In classic malignant hyperthermia, the initial signs are tachycardia, rapidly rising end-tidal $C0_2$, 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 CO_2 absorbent used in general anesthesia becomes activated and warm to the touch from the exothermic reaction with the CO_2 exhaled by the affected individual. The individual may display peripheral mottling and, on occasion, sweating and rarely cyanosis. Blood gas analysis usually reveals hypercarbia (P_{CO2}>60 mmHg) and respiratory and metabolic acidosis without oxygen desaturation. Elevation of end-tidal CO_2 greater than 55 mmHg 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 CO_2 retention and metabolic acidosis. Hyperkalemia, hypercalcemia, lactacidemia, and myoglobinuria are characteristic but are not present in every case. 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 [Fortunato et al 2000]. 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 malignant hyperthermia. Treatment with dantrolene results in much lower morbidity and mortality than first reported when MH was recognized in the 1960s [Larach et al 2008] but the 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, insufficient personnel, and/or 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).

Malignant hyperthermia 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 manifestation may depend on genetic predisposition, dose of trigger agents, or duration of exposure.

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

Malignant hyperthermia susceptibility (MHS) phenotypes. Several distinct clinical presentations predispose to classic MH:

- **Central core disease** and **multiminicore disease** are myopathies caused by mutation of *RYR1* (see Genetically Related Disorders).
- **King or King-Denborough syndrome** 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 [D'Arcy et al 2008, Dowling et al 2011].
- **Masseter muscle rigidity (MMR)**, or rigidity of the jaw muscles after administration of succinylcholine, presages clinical MH in up to 30% of cases. Even in the absence of clinical MH, myoglobinuria in individuals with MMR is common postoperatively. MMR probably occurs in individuals of all ages regardless of MHS status; however, MMR is more common in children, particularly following gas anesthesia induction.

Genotype-Phenotype Correlations

A limited number of studies have addressed genotype-phenotype correlations. See Robinson et al [2002], Robinson et al [2003], Carpenter et al [2009b].

Genotype-phenotype correlations in MHS are difficult to study. No correlation between genotype and clinical phenotype is apparent because CHCT/IVCT 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 recent study demonstrated that the *RYR1* pathogenic variants p.Arg163Cys, p.Arg2163His, p.Arg2435His, and p.Thr4826Ile were associated with higher CK concentrations than the pathogenic variant p.Gly2434Arg. Stronger contractures and shorter response times in the response to caffeine were also features of these pathogenic variants [Carpenter et al 2009b].

Correlations exist between genotype and halothane-caffeine induced contracture response:

- Analysis of 15 *RYR1* pathogenic variants showed a strong correlation ($r=0.95$, $p<0.001$) between the caffeine sensitivity of different *RYR1* pathogenic variants and the clinical IVCT [Tong et al 1997]. A good correlation was also observed between the caffeine threshold and tension values observed for 11 different *RYR1* pathogenic variants [Manning et al 1998b].
- Functional assays of different mutated RYR1 proteins expressed in skeletal muscle myotubes derived from *Ryr1* knock-out mice showed increased resting myoplasmic calcium levels and increased sensitivity of channels to activation by caffeine and subsequent depolarization [Yang et al 2003, Dirksen & Avila 2004, Yang et al 2007].
- The *RYR1* pathogenic variants associated with both MH and CCD (p.Arg163Cys, p.Arg2163His, and p.Arg2435His) exhibit more severe caffeine and halothane responses than those associated with MH alone [Robinson et al 2002].
- CHCT/IVCT results are stronger in males than females and are also affected by muscle size and viability.
- Individuals with the *RYR1* pathogenic variants p.Gly341Arg, p.Arg614Cys, and p.Gly2434Arg show weaker contraction results. Discordance in genotype-phenotype correlation is more common among these pathogenic variants [Robinson et al 2003].
- Swiss individuals with MHS showed stronger IVCT results for *RYR1* variants p.Arg614Cys and p.Val2168Met than for the variants p.Gly2434Arg and p.Arg2458Cys [Girard et al 2001].
- A single amino-acid deletion in *RYR1*, p.Glu2348del, was associated with unusually high contraction tension in two unrelated families with MHS [Sambuughin et al 2001a].

Penetrance

The penetrance of MH susceptibility is unknown. What is known is that up to 50% of individuals with MH susceptibility have undergone anesthesia uneventfully despite use of one of the agents known to trigger MH.

Anticipation

Anticipation is not observed.

Prevalence

The incidence of MH is best described by the reported incidence per anesthetic. Currently, 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 as 1:100,000 for adults [Brady et al 2009] and 3:100,000 in children [Li et al 2011]. Because many individuals undergoing surgery who experience marked hyperthermia may be coded as being MH susceptible, the exact incidence and prevalence has been difficult to clarify. It seems 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, as well as the prevalence of susceptibility variants in the population; Monnier et al [2002] estimate the prevalence of one of the causative variants at 1:2,000 to 1:3,000 individuals in the French population. Ibarra et al [2006] report similar numbers for the Japanese population.

Genetically Related (Allelic) Disorders

RYR1. Several distinct congenital myopathies, characterized by hypotonia and slowly progressive or non-progressive muscle weakness, are associated with pathogenic variants in *RYR1*. Some are inherited in an autosomal dominant manner, others in an autosomal recessive manner [Klein et al 2012]. These myopathies include central core disease (CCD), multiminicore disease (MmD), congenital fiber type disproportion, centronuclear myopathy (CNM), King-Denborough Syndrome (KDS), and nemaline myopathy (NM) [Robinson et al 2006, D'Arcy et al 2008, Clarke et al 2010, Wilmshurst et al 2010, Dowling et al 2011, Klein et al 2012, Kondo et al 2012]. Pathogenic variants in *RYR1* have also been linked to exertional/environmental heat stroke (EHS) [Hopkins et al 1991, Tobin et al 2001, Capacchione & Muldoon 2009, Nishio et al 2009, Groom et al 2011] and exercise-induced rhabdomyolysis [Wappler et al 2001, Davis et al 2002]. However, CCD and MmD are the most commonly associated disorders with dominant and recessive pathogenic variants in *RYR1*, respectively.

- **Central core disease (CCD)** is characterized by muscle weakness ranging from mild to severe. Most affected individuals have mild disease with symmetric proximal muscle weakness and variable involvement of facial and neck muscles. Motor development is usually delayed, but most affected individuals acquire independent ambulation. Life span is usually normal. 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. The outcome ranges from death in infancy to survival beyond age five years.

  The diagnosis of CCD is based on clinical findings of muscle weakness, the histopathologic findings of characteristic cores on muscle biopsy, and molecular genetic testing. About 90% of CCD cases are associated with mutation of *RYR1* [Wu et al 2006].

  CCD is generally inherited in an autosomal dominant manner, although families with autosomal recessive inheritance and many simplex cases (i.e., a single occurrence in a family) have been increasingly reported [McCarthy et al 2000, Jungbluth 2007, Zhou et al 2007, Monnier et al 2008, Klein et al 2012].

  More than 100 *RYR1* pathogenic variants have been associated with the autosomal

dominant or autosomal recessive forms of CCD, including small deletions, insertions, and splice site variants. The majority of allelic variants associated with CCD are missense variants clustered in the C-terminal domain of the protein, which comprises the transmembrane/luminal and pore-forming region of the channel.

Individuals with CCD are at increased risk for MHS.

- **Multiminicore disease (MmD)** is broadly classified into four groups: classic form, moderate form with hand involvement, antenatal form with arthrogryposis multiplex congenita (AMC), and ophthalmoplegic form. About 75% of affected individuals have classic MmD 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. Fewer than 10% of individuals have each of the other three forms.

  The diagnosis of MmD is based on the presence of multiple "minicores" visible on muscle biopsy oxidative stains. Minicores are small zones of sarcomeric disorganization and/or diminished oxidative activity that correlate with lack of mitochondria in muscle fibers. Because minicores are not specific to MmD, the diagnosis of MmD is based on the presence of minicores in a large proportion of muscle fibers associated with static or slowly progressive weakness and absence of findings diagnostic of other disorders.

  MmD is inherited in an autosomal recessive manner. Pathogenic variants in two genes, *SELENON* (*SEPN1*) and *RYR1*, account for about half the cases of MmD. Classic MmD with ophthalmoplegia and other clinical subgroups have been associated with homozygous and compound heterozygous pathogenic variants in *RYR1* [Jungbluth 2007, Monnier et al 2008, Jungbluth et al 2011].

  Individuals with MmD may be at increased risk for MH, although the evidence is sparse and there is no consensus as to the risk.

CACNA1S. Pathogenic variants are identified in *CACNA1S* in 70% of individuals meeting clinical diagnostic criteria for hypokalemic periodic paralysis (HypoPP). Two different forms of HypoPP are recognized: the paralytic form (75% of individuals) and the myopathic form with a slowly progressive fixed myopathy (25% of individuals). The paralytic form is characterized by attacks of reversible flaccid paralysis with concomitant hypokalemia, which usually leads to paraparesis or tetraparesis but spares the respiratory muscles and heart. Triggering factors consist mainly of carbohydrate-rich meals and rest after exercise. The myopathic form of HypoPP results in a progressive fixed muscle weakness that begins as exercise intolerance predominantly in the lower limbs at extremely variable ages. It occurs independent of paralysis and may be the sole manifestation of the disease.

The diagnosis of hypokalemic periodic paralysis rests on a history of episodes of flaccid paralysis, low serum concentration of potassium (<3.5 mmol/L) during attacks, the absence of myotonia clinically and on electromyography (EMG), and a family history consistent with autosomal dominant inheritance.

Hypokalemic periodic paralysis is inherited in an autosomal dominant manner.

The two reports suggesting a relationship between HypoPP 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. The combination of hypercarbia, muscle rigidity, tachycardia, hyperthermia, metabolic acidosis, and rhabdomyolysis during or shortly after anesthesia is distinctive for MH. Some syndromes share some elements of MH:

- **Sepsis** shares the constellation of hyperthermia, hypercarbia, and acidosis. However, rigidity is uncommon, as is marked elevation of serum CK concentration. Leukocytosis, which is typically present with sepsis, is uncommon in MH.
- **Overheating from aggressive heating measures** utilized during anesthesia, (especially in the pediatric population) causes hyperthermia, tachycardia, and sometimes acidosis.
- **Pheochromocytoma crisis** marked by hypertension, tachycardia, and sometimes fever has been mistaken for MH, particularly in the postoperative period. If beta blockade is used to treat the tachycardia, heart failure may result from unopposed alpha activity.
- **Ischemic encephalopathy** is manifest by failure to awaken from anesthesia, muscle rigidity sometimes progressing to opisthotonus, hyperthermia, and tachycardia. Seizures are common in this condition but not in MH.
- **Ascending tonic-clonic syndrome** follows intrathecal injection of a water-soluble, high ionic radiologic contrast agent. When the agent ascends into the cerebral ventricles, the individual displays ascending tonic-clonic activity leading to frank seizures, rigidity accompanied by fever, and acidosis if respiration is compromised.
- **Thyrotoxicosis** is marked by hyperthermia, hypercarbia, and tachycardia but not muscle rigidity.
- **Neuroleptic malignant syndrome (NMS)** has all the features of MH, including: muscle rigidity, rhabdomyolysis, acidosis, and fever, but is manifest after administration of neuroleptic agents such as atypical antipsychotics, haloperidol, and drugs used in the treatment of schizophrenia. Postmortem high-resolution melting followed by sequencing of selected exons of *RYR1* in 11 individuals who died of NMS revealed two pathogenic variant, one of which has previously been reported in individuals with MH [Sato et al 2010]. **Serotonin syndrome,** which is a rare reaction from serotonin uptake inhibitor drugs, displays similar signs. These syndromes occur in the non-anesthetized individual.
- **Dystrophinopathy** (Duchenne or Becker muscular dystrophy). Affected individuals are at increased risk for rhabdomyolysis and life-threatening hyperkalemia with cardiac arrest following administration of succinylcholine or potent volatile anesthetics. 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].

- **Myotonic syndromes** (myotonic dystrophy type 1, myotonic dystrophy type 2, myotonia congenita) can be associated with muscle rigidity mimicking MH after succinylcholine administration.

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].

Environmental/exertional heat stress (EHS). Recent clinical, genetic, and laboratory studies using animal models provide evidence for a relationship between environmental or exertional heat stress (EHS) and MH susceptibility [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 12-year-old boy 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 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].

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 exercise-induced rhabdomyolysis [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, and two previously MH-associated variants (p.Ala1352Gly and a 9-bp insertion in exon 91) in individuals with ER.

***RYR1* and other myopathies.** Underlying genetic changes in *RYR1* may predispose to other musculoskeletal disorders. A recent study identified a large number of novel *RYR1* allelic variants causing congenital myopathies with dominant or recessive inheritance [Klein et al 2012]. Another study by Li et al [2011] demonstrated an association between MH and other myopathies, especially muscular dystrophies. 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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with malignant hyperthermia susceptibility (MHS), the following evaluations are recommended if they have not already been completed:

- Arterial blood gas analysis; serum concentration of electrolytes, lactate, and CK; coagulation studies; presence of myoglobin in the urine and elevated myoglobin levels in serum.
- Continuous core temperature monitoring until the syndrome has resolved
- Measurement of serum CK concentrations until normalized
- Family history of anesthetic complications
- Once the syndrome has resolved, neurologic assessment for evidence of muscle damage
- Clinical genetics consultation

Treatment of Manifestations

For management guidelines, see Guidelines/Consensus Statements and Figure 2.

Figure 2.

MHAUS treatment guide for malignant hyperthermia
Copyright, The Malignant Hyperthermia Association of the United States (MHAUS)

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 CO_2.
- 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 RYR-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 patient is hyperthermic, administer iced solutions, ice packs to groin, axilla, and neck, nasogastric lavage with iced solution, or more aggressive measures as needed. 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. Check values 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 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 (AMRA) 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 or for any individual with an equivocal contracture test response (MHE) (treated clinically as MHS):

- 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 human malignant hyperthermia (MH) events.

- Individuals with any form of myotonia (see Differential Diagnosis) should not receive succinylcholine.
- Individuals with central core disease, multiminicore disease, 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, Turlock, California (www.medicalert.org).

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-anatagonist) 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].

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

If a pathogenic variant has been identified in the family, molecular genetic testing of at-risk relatives is warranted to identify those who also have the pathogenic variant and thus will benefit from avoiding anesthetic agents that increase the risk for a malignant hyperthermia episode.

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 MH-susceptible individual.

In the case of a fetus whose father is known to be MH susceptible but whose mother is not known to be MH susceptible, 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.

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 knock-out mouse model of MH. This finding is suggestive of possible effectiveness of AICAR in the prophylactic treatment of humans with enhanced susceptibility to exercise/ heat-induced sudden death associated with mutation of *RYR1*.

Search ClinicalTrials.gov for access to 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

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

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; the proportion of individuals with MHS caused by *de novo* variants is unknown.

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include contracture testing or molecular genetic testing, if available and if the pathogenic variant in the proband has been identified.

Note: Although most individuals diagnosed with MHS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or decreased penetrance of the MHS-causing allele.

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, the risk to the sibs is 50%.
- When the parents are clinically unaffected based on contracture testing and/or molecular genetic testing, the risk to the sibs of a proband appears to be low.
- If an MHS-causing variant cannot be detected in the genomic DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

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

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members 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.

Genetic heterogeneity. Even if the same pathogenic variant is not found in a family member of an individual with a causative variant, the family member may still be at risk for MH: in a few families, a family member has been found to have a variant different from that identified in the proband [Monnier et al 2003, Clarke et al 2010].

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 or clinical evidence of the disorder, it is likely that the proband has a *de novo* pathogenic variant. However, possible non-medical explanations, including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be considered.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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

Requests for prenatal testing for pharmacogenetic conditions which (like MH susceptibility) have effective treatment and prevention are not common. Prenatal testing is generally not offered. However, Girard et al [2006] reported a child diagnosed with MH based on molecular genetic testing on cord blood obtained at delivery.

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. P. Jane Halsall, 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.J.Halsall@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

- **My46 Trait Profile**
  Malignant hyperthermia susceptibility

- **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)
  Email: bwb@pitt.edu; mcl2@pitt.edu; adamskj2@upmc.edu
  www.mhreg.org

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

Locus Name	Gene	Chromosome Locus	Protein	Locus Specific	HGMD
MHS1	*RYR1*	19q13.2	Ryanodine receptor 1	Leiden Muscular Dystrophy pages (RYR1)	RYR1
MHS2	Unknown	17q11.2-q24	Unknown		
MHS3	Unknown	7q21.2	Unknown		
MHS4	Unknown	3q13.1	Unknown		
MHS5	*CACNA1S*	1q32.1	Voltage-dependent L-type calcium channel subunit alpha-1S	Calcium channel, voltage-dependent, L type, alpha 1S subunit (CACNA1S) @ LOVD	CACNA1S
MHS6	Unknown	5p	Unknown		

Data are compiled from the following standard references: gene from HGNC; chromosome locus, locus name, critical region, complementation group from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD) 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
601888	MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 6

Molecular Genetic Pathogenesis

A relationship between MH and environmental or exertional heat stroke has been corroborated using animal models of MH. It has long been known that pigs with MHS undergo lethal hypermetabolic episodes following prolonged elevations in ambient temperature. In addition, heat-induced MH reactions in the absence of triggering anaesthetics have been reported for heterozygous *RYR1* knock-in mice harboring either the p.Tyr522Ser [Chelu et al 2006] or p.Arg163Cys [Yang et al 2006] MHS-causing variant. The mechanism for enhanced temperature sensitivity of these mice was shown to result from S-nitrosylation of RYR1 increasing the temperature sensitivity of the release channel to activation, resulting in inappropriate channel openings and raised intracellular calcium levels [Durham et al 2008, Lanner et al 2012].

The MHS3 locus was linked to chromosome 7q21-q22. At this locus, the candidate gene *CACNA2D1*, which encodes a subunit of the L-type voltage-dependent calcium channel that is intimately associated at the skeletal muscle triadic junctions with the ryanodine receptor, had no pathogenic variants in a family linked to MHS3 [Schleithoff et al 1999]. Linkage to MHS3 was not confirmed in studies of other families with MHS and no *CACNA2D1* pathogenic variant has yet been found in association with MHS.

RYR1

Gene structure. *RYR1* consists of 106 exons (two of which are alternatively spliced) encompassing a total of 160 kb and produces one of the largest known proteins with 5038 amino acids. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. *RYR1* has at least 16 normal variants in the coding region [Gillard et al 1992, Brown et al 2000]. See Table 4.

Pathogenic variants. More than 300 pathogenic variants in *RYR1* have been associated with MHS and/or CCD. Most of the *RYR1* pathogenic variants are private (i.e., observed in only one or a few families); thus, pathogenic variant detection is a major challenge. Almost all MHS-causing variants are missense variants; however, an in-frame deletion of a single amino acid (p.Glu2348del) in the central region of RYR1 [Sambuughin et al 2005] and a single-nucleotide deletion at the extreme C-terminal end of the protein [Rossi et al 2007] have also been reported. See Table 4 and Table 5 (pdf).

Table 4.

RYR1 Variants Discussed in This *GeneReview*

View in own window

Variant Classification	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference	Ref Seq
Benign	c.2537C>T	p.Ser846Leu	Robinson et al [2006]	
	c.4767A>C	p.Gln1589Pro	Robinson et al [2006]	
	c.5360C>T	p.Pro1787Leu	Gillard et al [1992]	
	c.6178G>T	p.Gly2060Cys	Gillard et al [1992]	
	c.7648C>G	p.Val2550Leu	Monnier et al [2000]	
	c.10747G>C	p.Glu3583Gln	Robinson et al [2006]	
	c.11266C>G	p.Gln3756Glu	Brown et al [2000]	
	c.103T>C	p.Cys35Arg	Lynch et al [1997]	
	c.487C>T	p.Arg163Cys	Quane et al [1993]	
	c.488G>T	p.Arg163Leu	Monnier et al [2005]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. *RYR1* encodes the skeletal muscle calcium release channel located in the sarcoplasmic reticulum (SR) (also known as ryanodine receptor type 1). The functional channel is a homotetramer of 560-kd subunits and releases calcium stored in the SR in response to membrane depolarization transduced by the dihydropyridine receptor (DHPR). The cytoplasmic domain, also called the foot structure, is formed by the first approximately 4000 amino acids and bridges the gap between the SR and the transverse tubular membrane. The last 1000 amino acids form the transmembrane domain and contain the permeation pathway and pore of the channel [Ramachandran et al 2009].

Abnormal gene product. MHS-causing variants in *RYR1* cause Ca^{2+} release channels in the sarcoplasmic reticulum to exhibit an increased sensitivity to activation by both endogenous (e.g., voltage sensor) and exogenous (e.g., caffeine, halothane) triggers. This global hypersensitivity of

the SR Ca^{2+} mechanism predisposes skeletal muscle uncontrolled Ca^{2+} release during an MH event.

CACNA1S

Gene structure. The gene spans 90 kb and consists of 44 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A few dominant pathogenic variants have been identified in several families with MHS [Jurkat-Rott et al 2000, Carpenter et al 2009, Pirone et al 2010, Toppin et al 2010]. Three pathogenic variants (p.Arg1086His, p.Thr1354Ser, and p.Arg174Trp) have been functionally characterized [Weiss et al 2004, Pirone et al 2010, Eltit et al 2012]. See Table 6.

Table 6.

CACNA1S Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.3257G>A	p.Arg1086His	NM_000069.2 NP_000060.2
c.3256C>T	p.Arg1086Cys	
c.520C>T	p.Arg174Trp	
c.4060A>T	p.Thr1354Ser	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *CACNA1S* encodes the α1 subunit of the pentameric (α1, α2-δ, β, and γ) dihydropyridine receptor (DHPR, also termed voltage sensor or L-type calcium channel) in skeletal muscle. The skeletal muscle DHPR is located in the transverse tubule membrane and acts simultaneously as both a voltage sensor for activation of the SR ryanodine receptor and as a voltage-dependent L-type Ca^{2+} channel [Dirksen & Avila 2002]. The α1 subunit contains all the pore and gating structures of the channel and comprises four homologous repeats connected by large cytoplasmic loops. The fourth transmembrane segment of each repeat (S4) possesses positively charged amino acids approximately every third residue and contributes to the "voltage-sensing" region of the channel. Sarcolemmal depolarization during an action potential induces voltage-driven conformational changes in the S4 segments of the DHPR that rapidly trigger the opening of nearby SR Ca^{2+} release channels (ryanodine receptors or RyR1s). Although the intracellular loop that links the second and third repeat (II-III loop) plays a critical role in mechanical activation of RyR1 by the DHPR following depolarization [Nakai et al 1998], other regions of the DHPR α1 [Leong & MacLennan 1998] and β subunits [Cheng et al 2005] of the DHPR have also been suggested to interact with RyR1 and influence RyR1-mediated SR Ca^{2+} release [Eltit et al 2012].

Abnormal gene product. Three of the five identified MHS-causing variants in *CACNA1S* (p.Arg1086His, p.Arg1086Cys, and p.Arg1086Ser) result in mutation of a highly conserved

arginine residue in the intracellular loop linking repeats III and IV of the DHPR α1 subunit. Similar to that observed for MH-causing variants in *RYR1*, the p.Arg1086His pathogenic variant in *CACNA1S* increases the sensitivity of the SR Ca^{2+} release mechanism to activation by both caffeine and voltage [Weiss et al 2004]. A fourth *CACNA1S* pathogenic variant, p.Arg174Trp, was identified in a family with MH that does not harbor an *RYR1* pathogenic variant [Carpenter et al 2009a]. The p.Arg174Trp pathogenic variant was recently proposed to sensitize RyR1 to MH triggers by enhancing basal RyR1 Ca^{2+} leak out of the SR [Eltit et al 2012]. Finally, a p.Thr1354Ser pathogenic variant located in the IVS5-S6 extracellular pore-loop was shown to accelerate L-type Ca^{2+} current activation in addition to increasing the caffeine sensitivity of RyR1-mediated SR Ca^{2+} release [Pirone et al 2010].

Thus, MHS is similarly caused by pathogenic variants in *RYR1* (MHS1) and both the α1 (MHS5) and α2 δ subunits (MHS3) of the skeletal muscle DHPR, proteins that are each critically involved in coordinating the excitation-contraction process in skeletal muscle. This indicates that the pathogenesis of MH reflects a dysfunction in the muscle EC coupling process and that MHS resulting from mutation occurring at other loci (e.g., MHS2, MHS4, and MHS6) is likely to involve functional alterations to other protein members of the release complex.

Calsequestrin type 1 (calsequestrin-1) is an acidic, moderate-affinity, high-capacity Ca^{2+}-binding protein located in the terminal cisternae of the sarcoplasmic reticulum. The protein is encoded by *CASQ1* and functions to concentrate exchangeable Ca^{2+} ions near sites of RYR1-mediated Ca^{2+} release. Calsequestrin-1 is physically tethered to RYR1 via triadin and junctin, forming a quaternary RYR1-triadin-junctin-calsequestrin-1 complex that modulates the luminal Ca^{2+} sensitivity of the RYR1 Ca^{2+} release channel [Beard et al 2004]. Interestingly, genetically engineered mice lacking calsequestrin-1 develop normally, but when anesthetized with MH trigger agents such as halothane develop malignant hyperthermia. This finding indicates that intracellular hypercalcemia originating from many different fundamentally distinct etiologies can result in an MH response [Dainese et al 2009].

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