Malignant Hyperthermia Panel, Sequencing

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Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle calcium regulation which is triggered by volatile anesthetics, either with or without the depolarizing muscle relaxant succinylcholine. Less commonly, manifestations may be precipitated by strenuous exercise or high environmental temperatures. Excessive calcium release from the sarcoplasmic reticulum leads to disturbance of the intracellular calcium ion homeostasis causing skeletal muscle contraction and hypermetabolism. The hypermetabolic state generates heat and excess lactate and can result in hypercarbia, tachycardia, hyperkalemia, hyperthermia, acidosis, muscle rigidity, compartment syndrome, rhabdomyolysis, myoglobinuria, and potentially death. Episodes of MH require prompt diagnosis and treatment to reduce mortality. MH susceptibility may be assessed by functional laboratory testing (caffeine-halothane contracture test, otherwise known as in vitro contracture test) or molecular testing of MH-associated genes.

Featured ARUP Testing

Malignant Hyperthermia Panel, Sequencing
3002688

Method: Massively Parallel Sequencing

- Use to determine genetic etiology of MH susceptibility (MHS) in individuals with known or suspected clinical history of MH.
- Use to assess for MHS in healthy individuals with family history of MH.

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

Disease Overview

Epidemiology/Prevalence

Approximately 1 in 2,000 individuals has a pathogenic variant in an MH susceptibility gene.[1] As not all MH susceptible individuals are exposed to triggering agents, the estimated prevalence of anesthesia-related MH is 1-2 per 100,000.

Typical Testing Strategy

- Muscle biopsy and contracture testing is recommended for:
  - Individuals with suspected clinical history of MH
  - First-degree relatives of a proband with clinical history of MH, if proband cannot be tested or causative familial variant not known
  - At-risk family members when the MH-causing variant is not known
  - Individuals with suspected personal or known family history of MHS prior to military service
- Molecular MHS testing is recommended for:
  - Individuals with confirmed/suspected clinical MH event or positive contracture test
  - Relatives of individuals with a positive contracture test or known MHS variant
    - When the causative pathogenic MHS variant is known in the family, molecular testing can be used to identify relatives at increased risk for MHS. If the causative pathogenic MHS variant in the family is not known or a relative tests negative for a known familial variant, contracture testing is used to assess susceptibility.[1]

Additional Guidance

- A clinical grading scale has been proposed to assist in determining if an adverse anesthetic event is a clinical MH event.[2]
- The European Malignant Hyperthermia Group has released guidelines for the investigation of MH susceptibility.[3]
- Malignant Hyperthermia Association of the United States (MHAUS) has released treatment recommendations for MH.[4]
- MHAUS provides a list of biopsy centers that can perform contracture testing.[4]
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) Dosing Guideline recommends that halogenated volatile anesthetics and the depolarizing muscle relaxants succinylcholine are relatively contraindicated in persons with MHS.[5]

Genetics

Genes

RYR1, *CACNA1S*

Etiology

Pathogenic germline gain-of-function variants in the *RYR1* or *CACNA1S* genes

Penetrance

Incomplete

The overall penetrance is 40% for RYR1-associated MHS,[6] with a greater penetrance in males than in females. MH-susceptible individuals may have previous uneventful exposures to triggering anesthetics before developing an MH reaction. The probability of developing MH when exposed to triggers is 25% among all carriers of *RYR1* pathogenic variants but 76% among individuals who have experienced a previous MH reaction.[6]

Inheritance

Autosomal dominant

Test Description

Clinical Sensitivity

Up to 60% for MHS[7]

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%)	Analytic Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	99.9	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	99.9	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a diagnosis of MHS.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of targeted gene(s)
  - Regulatory region and deep intronic variants
  - Large deletions/duplications in any of the tested genes
  - Noncoding transcripts
  - RYR1 (NM_000540) exon 91 is not sequenced due to technical limitations of the assay
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Genes Tested			
Gene	MIM #	Associated Disorders	Inheritance
CACNA1S	114208	MHS 5 Hypokalemic periodic paralysis 1	AD
RYR1	180901	MHS 1	AD
		Central core disease	AD/AR
		Congenital neuromuscular disease with uniform type 1 fiber	AD/AR
		King-Denborough syndrome	AD
		Multiminicore myopathy	AR

AD, autosomal dominant; AR, autosomal recessive

References

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4. Malignant Hyperthermia Association of the United States. Accessed Aug 2020.
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6. Ibarra Moreno CA, Hu S, Kraeva N, et al. An assessment of penetrance and clinical expression of malignant hyperthermia in individuals carrying diagnostic ryanodine receptor 1 gene mutations. *Anesthesiology*. 2019;131(5):983-991.
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