

Variant: NM_000540.2(RYR1):c.455C>A (p.Ala152Asp)

Version: 2.0

CA405676716 [↗](#)

448182 (ClinVar) [↗](#)

Gene: RYR1 ([HGNC:6261](#))

Condition: malignant hyperthermia, susceptibility to, 1 ([MONDO:0007783](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: c0c0226a-09fa-41b5-af2b-4ce5b026f17b

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HGVS expressions

NM_000540.2(RYR1):c.455C>A (p.Ala152Asp)

NM_000540.2:c.455C>A

NC_000019.10:g.38444179C>A

CM000681.2:g.38444179C>A

NC_000019.9:g.38934819C>A

CM000681.1:g.38934819C>A

NC_000019.8:g.43626659C>A

NG_008866.1:g.15480C>A

ENST00000599547.6:c.455C>A

ENST00000359596.8:c.455C>A

ENST00000355481.8:c.455C>A

ENST00000359596.7:c.455C>A

ENST00000360985.7:c.455C>A

NM_001042723.1:c.455C>A

NM_000540.3:c.455C>A

NM_001042723.2:c.455C>A

Likely Pathogenic

Met criteria codes **3**

PS4_Moderate

PP3_Moderate

PM1

Evidence Links **0**

Expert Panel

[Malignant Hyperthermia Susceptibility VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Malignant Hyperthermia Susceptibility Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RYR1 Version 2

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Malignant Hyperthermia Susceptibility VCEP

This pathogenicity assessment is relevant only for malignant hyperthermia susceptibility (MHS) inherited in an autosomal dominant pattern. Variants in RYR1 can also cause other myopathies inherited in an autosomal dominant pattern or in an autosomal recessive

pattern. Some of these disorders may predispose individuals to malignant hyperthermia. RYR1 variants may also contribute to a malignant hyperthermia reaction in combination with other genetic and non-genetic factors and the clinician needs to consider such factors in making management decisions. This sequence variant predicts a substitution of alanine with aspartic acid at codon 152 of the RYR1 protein, p.(Ala152Asp). This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in two individuals with a personal or family history of an MH episode and positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) results (if the proband was unavailable for testing, a positive diagnostic test result in a mutation-positive relative was counted), PS4_Moderate (PMID:30236257, PMID:41153347). No functional studies were identified for this variant. This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704). A REVEL score >0.85 (0.9) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as Likely Pathogenic. Criteria implemented: PS4_Moderate, PM1, PP3_Moderate.

Met criteria codes

PS4_Moderate			This variant has been reported in two individuals with a personal or family history of an MH episode and positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) results (if the proband was unavailable for testing, a positive diagnostic test result in a mutation-positive relative was counted), PS4_Moderate (PMID:30236257, PMID:41153347).
PP3_Moderate			A REVEL score >0.85 (0.9) supports a pathogenic status for this variant, PP3_Moderate.
PM1			This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).

Curation History

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Showing 1 to 3 of 3 rows

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.