

Variant: *NM_001042723.2:c.7355G>C*

Version: 2.2

CA405669968 [↗](#)

1210314 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 0696ef53-ca1c-4130-8c3a-ded2439659dd

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HGVS expressions

NM_001042723.2:c.7355G>C

NC_000019.10:g.38500637G>C

CM000681.2:g.38500637G>C

NC_000019.9:g.38991277G>C

CM000681.1:g.38991277G>C

NC_000019.8:g.43683117G>C

NG_008866.1:g.71938G>C

ENST00000599547.6:c.7355G>C

ENST00000359596.8:c.7355G>C

ENST00000355481.8:c.7355G>C

ENST00000359596.7:c.7355G>C

ENST00000360985.7:c.7352G>C

ENST00000594335.5:c.807G>C

NM_000540.2:c.7355G>C

NM_001042723.1:c.7355G>C

NM_000540.3:c.7355G>C

Uncertain Significance

Met criteria codes **3**

PM1_Supporting

PP3_Moderate

PM5_Supporting

Not Met criteria codes **1**

PS4

Evidence Links **0**

Expert Panel

Malignant Hyperthermia Susceptibility VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) 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 arginine with proline at codon 2452 of the RYR1 protein, p. (Arg2452Pro). This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant was reported in an individual who had a positive in vitro contracture test (IVCT) result, however, it was not clear that the individual had a personal or family history of an MH event and therefor PS4 was not implemented (PMID:19191333). 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, use PM1_Supporting to avoid overweighting with PM5 (PMID: 21118704). Another variant assessed as likely pathogenic occurs at this codon, p. (Arg2452Trp), PM5_Supporting (PMID:30236257). A REVEL score >0.85 (0.953) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as a Variant of Uncertain Significance. Criteria implemented: PM1_Supporting, PM5_Supporting, PP3_Moderate.

Met criteria codes

PM1_Supporting This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, use PM1_Supporting to avoid overweighting with PM5 (PMID: 21118704).

PP3_Moderate   A REVEL score >0.85 (0.953) supports a pathogenic status for this variant, PP3_Moderate.

PM5_Supporting   Another variant assessed as likely pathogenic occurs at this codon, p.(Arg2452Trp), PM5_supporting (PMID:30236257).

Not Met criteria codes

PS4			This variant was reported in an individual who had a positive in vitro contracture test (IVCT) result, however, it was not clear that the individual had a personal or family history of an MH event and therefor PS4 was not implemented (PMID:19191333).
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Curation History



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