

Variant: *NM_000540.2(RYR1):c.6387C>G (p.Asp2129Glu)*

Version: 1.1

CA024575 [↗](#)

133157 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 5a4b773d-c1da-4b68-8673-530ad93f2fee

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HGVS expressions

NM_000540.2:c.6387C>G

NM_000540.2(RYR1):c.6387C>G (p.Asp2129Glu)

NC_000019.10:g.38494464C>G

CM000681.2:g.38494464C>G

NC_000019.9:g.38985104C>G

CM000681.1:g.38985104C>G

NC_000019.8:g.43676944C>G

NG_008866.1:g.65765C>G

ENST00000599547.6:c.6387C>G

ENST00000359596.8:c.6387C>G

ENST00000355481.8:c.6387C>G

ENST00000359596.7:c.6387C>G

ENST00000360985.7:c.6384C>G

NM_001042723.1:c.6387C>G

NM_000540.3:c.6387C>G

NM_001042723.2:c.6387C>G

Likely Pathogenic

Met criteria codes **3**

PP1_Moderate

PS4_Moderate

PM1

Not Met criteria codes **4**

BS1

BP4

BA1

PP3

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 aspartic acid with glutamic acid at codon 2129 of the RYR1

protein, p.Asp2129Glu. 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 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, both of these individuals had a positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) result (if the proband was unavailable for testing, a positive diagnostic test result in a mutation-positive relative was counted), PS4_Moderate (PMID:12059893, PMID:24433488). 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). This variant segregates with MHS in 6 individuals, PP1_Moderate (PMID:12059893, PMID:11241852). A REVEL score of 0.683 supports neither a pathogenic nor a benign status for this variant. This variant has been classified as Likely Pathogenic. Criteria implemented: PS4_Moderate, PM1, PP1_Moderate.

Met criteria codes

PP1_Moderate			This variant segregates with MHS in 6 individuals, PP1_Moderate (PMID:12059893, PMID:11241852).
PS4_Moderate			This variant has been reported in two unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, both of these individuals had a positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) result (if the proband was unavailable for testing, a positive diagnostic test result in a mutation-positive relative was counted), PS4_Moderate (PMID:12059893, PMID:24433488).
PM1			This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			A REVEL score of 0.683 supports neither a pathogenic nor a benign status for this variant.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			A REVEL score of 0.683 supports neither a pathogenic nor a benign status for this variant.

Curation History 

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