The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001042723.2:c.533A>G

Version: 1.1

CA405677115

1330371 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia of anesthesia (MONDO:0018493)
Inheritance Mode: Autosomal dominant inheritance
UUID: c6c2b3b8-5251-442f-aaae-d5dfe9ced9bb
Approved on: 2023/4/6
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HGVS expressions

NM_001042723.2:c.533A>G
NC_000019.10:g.38444257A>G
CM000681.2:g.38444257A>G
NC_000019.9:g.38934897A>G
CM000681.1:g.38934897A>G
NC_000019.8:g.43626737A>G
NG_008866.1:g.15558A>G
ENST00000599547.6:c.533A>G
ENST00000359596.8:c.533A>G
ENST00000355481.8:c.533A>G
ENST00000359596.7:c.533A>G
ENST00000360985.7:c.533A>G
NM_000540.2:c.533A>G
NM_001042723.1:c.533A>G
NM_000540.3:c.533A>G

Likely Pathogenic

Met criteria codes 5

PS2_Moderate PM1 PP3_Moderate PP1 PS4_Supporting

Not Met criteria codes 4

BA1 BS1 BP4 PS3

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 tyrosine with cysteine at codon 178 of the RYR1 protein, p.

(Tyr178Cys). This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in an individual with a personal or family history of an MH episode and 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_Supporting (PMID:16163667). In one individual the variant was determined to be de novo with confirmed parentage, PS2_Moderate. 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 three individuals, PP1 (PMID:16163667). A REVEL score >0.85 (0.951) supports a pathogenic status for this variant, PP3_Moderate. Based on using Bayes to combine criteria this variant is assessed as Likely Pathogenic, (PMID: 29300386). Criteria implemented: PS2_Moderate, PS4_Supporting, PM1, PP1, PP3_Moderate.

Met criteria codes

PS2_Moderate	✔	In one individual the variant was determined to be de novo with confirmed parentage, PS2_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).
PP3_Moderate	✔	A REVEL score >0.85 (0.951) supports a pathogenic status for this variant, PP3_Moderate.
PP1	✔	This variant segregates with MHS in three individuals, PP1_Supporting (PMID:16163667).
PS4_Supporting	✔	This variant has been reported in an individual with a personal or family history of an MH episode and 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_Supporting (PMID:16163667).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	✖	No functional studies were identified for this variant.

Curation History

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