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_000540.3(RYR1):c.7300G>A (p.Gly2434Arg)

CA024747

12970 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1436fa1b-2178-480a-9711-337815571f93
Approved on: 2022-07-11
Published on: 2022-07-11

HGVS expressions

NM_000540.3:c.7300G>A
NM_000540.3(RYR1):c.7300G>A (p.Gly2434Arg)
NC_000019.10:g.38499993G>A
CM000681.2:g.38499993G>A
NC_000019.9:g.38990633G>A
CM000681.1:g.38990633G>A
NC_000019.8:g.43682473G>A
NG_008866.1:g.71294G>A
ENST00000599547.6:n.7300G>A
ENST00000359596.8:c.7300G>A
ENST00000355481.8:c.7300G>A
ENST00000359596.7:n.7300G>A
ENST00000360985.7:c.7297G>A
ENST00000594335.5:n.752G>A
NM_000540.2:c.7300G>A
NM_001042723.1:c.7300G>A
NM_001042723.2:c.7300G>A

Pathogenic

The Expert Panel has overridden the computationally generated classification - "*Uncertain Significance - Conflicting Evidence*"

Met criteria codes 6

PP3_Moderate BS2 PS3 PS4 PM1 PP1_Strong

Not Met criteria codes 2

BA1 BS1

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 glycine with arginine at codon 2434 of the RYR1 protein, p.(Gly2434Arg). The maximum allele frequency for this variant among the six major gnomAD populations is NFE: 0.000078, a frequency consistent with pathogenicity for MHS. This variant has been reported in 178 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, 174 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 (PMID: 30236257, 10484775, 23558838, 16163667, 21455645, 23842196, 7849712, 7881417, 11575529, 15731587, 11668625, 12059893, 12151923, 31559918, 10700782, 17081125, 18564801, 20681998, 21965348, 23460944, 25735680, 25960145, 9030597, 25268394, 17667681). This variant has been identified in six individuals with negative IVCT/CHCT results, BS2 (PMID:30236257). A functional study in HEK293 cells shows an increased sensitivity to RYR1 agonists (PMID: 27586648). p.(Gly2434Arg) knock-in mice are susceptible to malignant hyperthermia due to volatile anesthetics and ex vivo assays demonstrate increased sensitivity to RYR1 agonists for knock-in myotubes, PS3 (PMID:30236258). 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 at least 20 individuals, PP1_Strong (PMID: 7849712, 11575529, 12059893, 25960145). A REVEL score >0.85 (0.956) supports a pathogenic status for this variant, PP3_Moderate. Based on using Bayes to combine criteria this variant is assessed as Pathogenic, (PMID: 29300386). Criteria implemented: PS3, PS4, PM1, PP1_Strong, PP3_Moderate, BS2.

Met criteria codes

PP3_Moderate	✔	A REVEL score >0.85 (0.956) supports a pathogenic status for this variant, PP3_Moderate.
BS2	✔	This variant has been identified in six individuals with negative IVCT/CHCT results, BS2 (PMID:30236257).
PS3	✔	A functional study in HEK293 cells shows an increased sensitivity to RYR1 agonists (PMID: 27586648). p.(Gly2434Arg) knock-in mice are susceptible to malignant hyperthermia due to volatile anesthetics and ex vivo assays demonstrate increased sensitivity to RYR1 agonists for knock-in myotubes, PS3 (PMID:30236258).
PS4	✔	This variant has been reported in 178 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, 174 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 (PMID: 30236257, 10484775, 23558838, 16163667, 21455645, 23842196, 7849712, 7881417, 11575529, 15731587, 11668625, 12059893, 12151923, 31559918, 10700782, 17081125, 18564801, 20681998, 21965348, 23460944, 25735680, 25960145, 9030597, 25268394, 17667681).
PM1	✔	This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).
PP1_Strong	✔	This variant segregates with MHS in at least 20 individuals, PP1_Strong (PMID: 7849712, 11575529, 12059893, 25960145).

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

Curation History

Showing 1 to 1 of 1 rows