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.7292A>T

Version: 2.0

CA405669526

1210302 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: ae4182ee-ab3b-4c07-b7e2-18de6c295040
Approved on: 2026/6/18
Published on: 2026/6/18

HGVS expressions

NM_001042723.2:c.7292A>T
NC_000019.10:g.38499985A>T
CM000681.2:g.38499985A>T
NC_000019.9:g.38990625A>T
CM000681.1:g.38990625A>T
NC_000019.8:g.43682465A>T
NG_008866.1:g.71286A>T
ENST00000599547.6:c.7292A>T
ENST00000359596.8:c.7292A>T
ENST00000355481.8:c.7292A>T
ENST00000359596.7:c.7292A>T
ENST00000360985.7:c.7289A>T
ENST00000594335.5:c.744A>T
NM_000540.2:c.7292A>T
NM_001042723.1:c.7292A>T
NM_000540.3:c.7292A>T

Likely Pathogenic

Met criteria codes 5

PP3_Moderate PS4_Moderate PM1_Supporting PM5_Supporting PS3_Moderate

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 aspartic acid with valine at codon 2431 of the RYR1 protein, p.(Asp2431Val). This variant was not present in a large population database (gnomAD v4.1.0) at the time this variant was classified. This variant has been reported in three unrelated individuals who had a personal or family history of a malignant hyperthermia reaction, two 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 variant-positive relative was counted), PS4_Moderate (PMID: 30236257; 41153347; 41339169). Functional studies in HEK293 cells showed an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID: 41339169). 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.(Asp2431Asn), PM5_Supporting. A REVEL score >0.85 (0.952) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as Likely Pathogenic. Criteria implemented: PS3_Moderate, PS4_Moderate, PM1_Supporting, PM5_Supporting, PP3_Moderate.

Met criteria codes

PP3_Moderate	✔	A REVEL score >0.85 (0.952) supports a pathogenic status for this variant, PP3_Moderate.
PS4_Moderate	✔	This variant has been reported in three unrelated individuals who had a personal or family history of a malignant hyperthermia reaction, two 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 variant-positive relative was counted), PS4_Moderate (PMID: 30236257; 41153347; 41339169).
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).
PM5_Supporting	✔	Another variant assessed as likely pathogenic occurs at this codon, p.(Asp2431Asn), PM5_Supporting.
PS3_Moderate	✔	Functional studies in HEK293 cells showed an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID: 41339169).

Curation History

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