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_000540.2(RYR1):c.11958C>G (p.Asp3986Glu)

Version: 2.0

CA023951

133026 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 71a97107-eb35-424a-b0bd-22b0f158fe29
Approved on: 2026/3/3
Published on: 2026/3/3

HGVS expressions

NM_000540.2(RYR1):c.11958C>G (p.Asp3986Glu)
NM_000540.2:c.11958C>G
NC_000019.10:g.38543821C>G
CM000681.2:g.38543821C>G
NC_000019.9:g.39034461C>G
CM000681.1:g.39034461C>G
NC_000019.8:g.43726301C>G
NG_008866.1:g.115122C>G
ENST00000688602.1:c.368C>G
ENST00000689936.1:c.350C>G
ENST00000359596.8:c.11958C>G
ENST00000355481.8:c.11943C>G
ENST00000359596.7:c.11958C>G
ENST00000360985.7:c.11940C>G
ENST00000593322.1:c.567C>G
ENST00000594335.5:c.5327C>G
NM_001042723.1:c.11943C>G
NM_000540.3:c.11958C>G
NM_001042723.2:c.11943C>G

Likely Pathogenic

Met criteria codes 3

PS4 BS3_Supporting PP1_Strong

Not Met criteria codes 5

PP3 PM1 BA1 BS1 BP4

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 glutamic acid at codon 3986 of the RYR1 protein, p.(Asp3986Glu). This variant is not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in ten unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, all 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; PMID:23558838). Functional studies in HEK293 cells do not show an increased sensitivity to RYR1 agonists, BS3_Supporting (PMID: 28403410). This variant does not reside in a hotspot for pathogenic variants that contribute to MHS. This variant segregates with MHS in seven individuals/families, PP1_Strong (PMID:28403410, UK (Leeds) MH Unit). A REVEL score of 0.763 supports neither a pathogenic nor a benign status for this variant. This variant has been classified as a Likely Pathogenic. Criteria implemented: PS4, PP1_Strong, BS3_Supporting.

Met criteria codes

PS4	✔	This variant has been reported in ten unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, all 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; PMID:23558838).
BS3_Supporting	✔	Functional studies in HEK293 cells do not show an increased sensitivity to RYR1 agonists, BS3_Supporting (PMID: 28403410).
PP1_Strong	✔	This variant segregates with MHS in seven individuals/families, PP1_Supporting (PMID:28403410, UK (Leeds) MH Unit).

Not Met criteria codes

PP3	✖	A REVEL score of 0.763 supports neither a pathogenic nor a benign status for this variant.
PM1	✖	This variant does not reside in a hotspot for pathogenic variants that contribute to MHS.
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	✖	A REVEL score of 0.763 supports neither a pathogenic nor a benign status for this variant.

Curation History

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.