

Variant: *NM_000540.2(RYR1):c.1565A>G (p.Tyr522Cys)*

Version: 1.2

CA024287 [↗](#)

133100 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: ae0ee76e-fd29-4011-ba36-191fd822a3b3

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HGVS expressions

NM_000540.2:c.1565A>G

NM_000540.2(RYR1):c.1565A>G (p.Tyr522Cys)

NC_000019.10:g.38455359A>G

CM000681.2:g.38455359A>G

NC_000019.9:g.38945999A>G

CM000681.1:g.38945999A>G

NC_000019.8:g.43637839A>G

NG_008866.1:g.26660A>G

ENST00000599547.6:c.1565A>G

ENST00000359596.8:c.1565A>G

ENST00000355481.8:c.1565A>G

ENST00000359596.7:c.1565A>G

ENST00000360985.7:c.1565A>G

NM_001042723.1:c.1565A>G

NM_000540.3:c.1565A>G

NM_001042723.2:c.1565A>G

Likely Pathogenic

Met criteria codes 4

PS4_Moderate

PM1_Supporting

PP3_Moderate

PM5

Not Met criteria codes 5

BS1

BS3

BP4

PS3

BA1

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 522 of the RYR1 protein, p.Tyr522Cys. This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in four unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, one 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:30236257, PMID:16244001, PMID:32919876). Studies in HEK293 cells demonstrated a leaky channel and neither PS3 or BS3 were awarded (PMID:26115329, PMID:31841587). Another variant assessed as pathogenic occurs at this codon, p.(Tyr522Ser), PM5. 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). A REVEL score >0.85 (0.949) supports a pathogenic status for this variant, PP3_Moderate. This variant is classified as Likely Pathogenic. Criteria implemented: PS4_Moderate, PM1_Supporting, PM5, PP3_Moderate.

Met criteria codes

PS4_Moderate			This variant has been reported in four unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, one 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:30236257, PMID:16244001, PMID:32919876).
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).
PP3_Moderate			A REVEL score >0.85 (0.949) supports a pathogenic status for this variant, PP3_Moderate.
PM5			Another variant has been assessed as pathogenic occurs at this codon, p.(Tyr522Ser), PM5.

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			Studies in HEK293 cells demonstrated a leaky channel and neither PS3 or BS3 were awarded (PMID:26115329, PMID:31841587).
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			Studies in HEK293 cells demonstrated a leaky channel and neither PS3 or BS3 were awarded (PMID:26115329, PMID:31841587).
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 3 of 3 rows

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