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.1654C>T (p.Arg552Trp)

Version: 1.1

CA024299

133106 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: ffa322ea-bab6-4498-82a7-a256314a053e
Approved on: 2023/4/6
Published on: 2023/4/6

HGVS expressions

NM_000540.3(RYR1):c.1654C>T (p.Arg552Trp)
NM_000540.3:c.1654C>T
NC_000019.10:g.38455528C>T
CM000681.2:g.38455528C>T
NC_000019.9:g.38946168C>T
CM000681.1:g.38946168C>T
NC_000019.8:g.43638008C>T
NG_008866.1:g.26829C>T
ENST00000599547.6:c.1654C>T
ENST00000359596.8:c.1654C>T
ENST00000355481.8:c.1654C>T
ENST00000359596.7:c.1654C>T
ENST00000360985.7:c.1654C>T
NM_000540.2:c.1654C>T
NM_001042723.1:c.1654C>T
NM_001042723.2:c.1654C>T

Likely Pathogenic

Met criteria codes 4

PS4_Moderate PP1 PM1 PS3_Moderate

Not Met criteria codes 4

PP3 BA1 BS1 BP4

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 Arginine with Tryptophan at codon 552 of the RYR1 protein, p.(Arg552Trp). The maximum allele frequency for this variant among the six major gnomAD populations is AMR: 0.00003, a frequency consistent with pathogenicity for MHS. This variant has been reported in 6 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, 5 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:9138151, PMID:16244001). This variant segregates with MHS in three families, PP1 (PMID:30236257). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:9334205). This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704). A REVEL score of 0.83 supports neither a pathogenic nor a benign status for this variant. implemented: PS4_Moderate, PS3_Moderate, PM1, PP1.

Met criteria codes

PS4_Moderate	✔	This variant has been reported in 6 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, 5 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:9138151, PMID:16244001).
PP1	✔	This variant segregates with MHS in three families, PP1 (PMID:30236257).
PM1	✔	This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).
PS3_Moderate	✔	Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:9334205).

Not Met criteria codes

PP3	✖	A REVEL score of 0.83 supports neither a pathogenic nor a benign status for this variant.
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

Curation History

Showing 1 to 2 of 2 rows

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