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.130C>T (p.Arg44Cys)

Version: 1.1

CA024034

133045 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1eca410d-5681-4ef6-a109-45927d4ba949
Approved on: 2023/4/6
Published on: 2023/4/6

HGVS expressions

NM_000540.3(RYR1):c.130C>T (p.Arg44Cys)
NM_000540.3:c.130C>T
NC_000019.10:g.38440829C>T
CM000681.2:g.38440829C>T
NC_000019.9:g.38931469C>T
CM000681.1:g.38931469C>T
NC_000019.8:g.43623309C>T
NG_008866.1:g.12130C>T
ENST00000599547.6:c.130C>T
ENST00000359596.8:c.130C>T
ENST00000355481.8:c.130C>T
ENST00000359596.7:c.130C>T
ENST00000360985.7:c.130C>T
NM_000540.2:c.130C>T
NM_001042723.1:c.130C>T
NM_001042723.2:c.130C>T

Likely Pathogenic

Met criteria codes 4

PM1 PP3_Moderate PS3_Moderate PS4_Moderate

Not Met criteria codes 4

BA1 BS1 BS3 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 cysteine at codon 44 of the RYR1 protein, p.(Arg44Cys). The maximum allele frequency for this variant among the six major gnomAD populations is AMR: 0.000029, a frequency consistent with pathogenicity for MHS. This variant has been reported in two unrelated individuals who have a personal or family history of a malignant hyperthermia reaction and a positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) result (when the proband was unavailable for testing a positive diagnostic test result in a mutation positive relative was counted), PS4_Moderate (PMID:12709367, PMID:24433488). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:23459219). 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 > 0.85 supports pathogenicity, PP3_Moderate. For these reasons, this variant has been classified as Likely Pathogenic. Criteria implemented: PS4_Moderate, PS3_Moderate, PM1, PP3_Moderate.

Met criteria codes

PM1	✔	N-terminal hotspot region.
PP3_Moderate	✔	REVEL > 0.85
PS3_Moderate	✔	Decreased EC50 as compared to WT, 4-CmC
PS4_Moderate	✔	Two unrelated individuals, MH reactions and diagnostics tests.

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
BS3	✖	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

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.