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Variant: NM_000540.3(RYR1):c.1840C>T (p.Arg614Cys)

Version: 1.0

CA024311

12964 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: db1e9a13-5143-462b-8d02-86b85ab5b1c4
Approved on: 2021/3/17
Published on: 2021/3/31

HGVS expressions

NM_000540.3(RYR1):c.1840C>T (p.Arg614Cys)
NM_000540.3:c.1840C>T
NC_000019.10:g.38457545C>T
CM000681.2:g.38457545C>T
NC_000019.9:g.38948185C>T
CM000681.1:g.38948185C>T
NC_000019.8:g.43640025C>T
NG_008866.1:g.28846C>T
ENST00000599547.6:c.1840C>T
ENST00000359596.8:c.1840C>T
ENST00000355481.8:c.1840C>T
ENST00000359596.7:c.1840C>T
ENST00000360985.7:c.1840C>T
NM_000540.2:c.1840C>T
NM_001042723.1:c.1840C>T
NM_001042723.2:c.1840C>T

Pathogenic

Met criteria codes 6

PM5 PP3_Moderate PP1_Strong PS3_Moderate BS2_Supporting PS4

Not Met criteria codes 3

PM1 BA1 BS1

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 Cysteine at codon 614 of the RYR1 protein, p.(Arg614Cys). The maximum allele frequency for this variant among the six major gnomAD populations is NFE: 0.00019, a frequency consistent with pathogenicity for MHS. This variant has been reported in over 100 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, over 100 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:24433488, PMID:16163667, PMID:30236257, and others). This variant has been identified in an individual with negative IVCT/CHCT results, BS2_Moderate (PMID:10484775). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:26115329). This variant does not reside in a hotspot for pathogenic variants that contribute to MHS (PMID: 21118704). Another variant that has been assessed as pathogenic occurs at this codon, p.(Arg614Leu), PM5 (PMID:16917943). p.(Arg614Cys) segregates with MHS in 38 individuals PP1_Strong, (PMID:25960145, PMID:7586638, PMID:11493496 and others). A REVEL score >0.85 supports a pathogenic status for this variant, PP3_Moderate. Criteria implemented: PS3_Moderate, PS4, PM5, PP1_Strong, PP3_Moderate, BS2_Moderate. Based on using Bayes to combine criteria this variant is assessed as Pathogenic, (PMID: 29300386).

Met criteria codes

PM5	✔	Another variant that has been assessed as pathogenic occurs at this codon, p.(Arg614Leu), PM5 (PMID:16917943).
PP3_Moderate	✔	A REVEL score >0.85 supports a pathogenic status for this variant, PP3_Moderate.
PP1_Strong	✔	p.(Arg614Cys) segregates with MHS in 38 individuals PP1_Strong, (PMID:25960145, PMID:7586638, PMID:11493496 and others).
PS3_Moderate	✔	Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:26115329).
BS2_Supporting	✔	This variant has been identified in an individual with negative IVCT/CHCT results, BS2_Moderate (PMID:10484775).
PS4	✔	This variant has been reported in over 100 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, over 100 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:24433488, PMID:16163667, PMID:30236257, and others).

Not Met criteria codes

PM1	✖	This variant does not reside in a hotspot for pathogenic variants that contribute to MHS (PMID: 21118704).
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

Curation History

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