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Variant: NM_000540.3(RYR1):c.1201C>T (p.Arg401Cys)

Version: 1.0

CA023956

133029 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 61f449cf-05e9-4bd2-b696-05dcefd57769
Approved on: 2022/3/29
Published on: 2022/3/29

HGVS expressions

NM_000540.3:c.1201C>T
NM_000540.3(RYR1):c.1201C>T (p.Arg401Cys)
NC_000019.10:g.38451842C>T
CM000681.2:g.38451842C>T
NC_000019.9:g.38942482C>T
CM000681.1:g.38942482C>T
NC_000019.8:g.43634322C>T
NG_008866.1:g.23143C>T
ENST00000599547.6:c.1201C>T
ENST00000359596.8:c.1201C>T
ENST00000355481.8:c.1201C>T
ENST00000359596.7:c.1201C>T
ENST00000360985.7:c.1201C>T
NM_000540.2:c.1201C>T
NM_001042723.1:c.1201C>T
NM_001042723.2:c.1201C>T

Pathogenic

Met criteria codes 6

PM1_Supporting | PP1 | PM5 | PS3_Moderate | PP3_Moderate | PS4_Moderate

Not Met criteria codes 3

BA1 | BS1 | BP4

Evidence Links 1

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 401 of the RYR1 protein p.(Arg401Cys). The maximum allele frequency for this variant among the six major gnomAD populations is EAS: 0.00005, a frequency consistent with pathogenicity for MHS. This variant has been reported in five 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:30236257, PMID:12434264, PMID:24433488, PMID:25735680). This variant segregates with MHS in three individuals, PP1 (PMID:12066726, PMID:18564801). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists PS3_Moderate, (PMID:23459219). Another variant has been assessed as pathogenic occurs at this codon, p.(Arg401His), PM5 (PMID:16917943). 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 (0.886) supports pathogenicity, PP3_Moderate. Criteria implemented: PS4_Moderate, PS3_Moderate, PM1_Supporting, PM5, PP1, PP3_Moderate. Based on using Bayes to combine criteria this variant is assessed as Pathogenic, (PMID: 29300386).

Met criteria codes

PM1_Supporting	✔	N-terminal hotspot. Use PM1_Supporting to avoid overweighting with PM5
PP1	✔	This variant segregates with MHS in three individuals, PP1 (PMID:12066726, PMID:18564801).
PM5	✔	p.(Arg401His) assessed as pathogenic
PS3_Moderate	✔	HEK293 assay HEK293 assay PubMed:23459219
PP3_Moderate	✔	REVEL > 0.85
PS4_Moderate	✔	Five unrelated probands reported with malignant hyperthermia and positive IVCT/CHCT diagnostic test.

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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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