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Variant: NM_000540.2(RYR1):c.1597C>T (p.Arg533Cys)

Version: 1.0

CA024293

133102 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 5ac26bd0-a5a1-4e1c-99c8-8fd8264d8656
Approved on: 2021/3/17
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HGVS expressions

NM_000540.2:c.1597C>T
NM_000540.2(RYR1):c.1597C>T (p.Arg533Cys)
NC_000019.10:g.38455471C>T
CM000681.2:g.38455471C>T
NC_000019.9:g.38946111C>T
CM000681.1:g.38946111C>T
NC_000019.8:g.43637951C>T
NG_008866.1:g.26772C>T
ENST00000599547.6:c.1597C>T
ENST00000359596.8:c.1597C>T
ENST00000355481.8:c.1597C>T
ENST00000359596.7:c.1597C>T
ENST00000360985.7:c.1597C>T
NM_001042723.1:c.1597C>T
NM_000540.3:c.1597C>T
NM_001042723.2:c.1597C>T

Pathogenic

Met criteria codes 5

PM1 PS3_Moderate PS4_Supporting PP1_Strong PP3_Moderate

Not Met criteria codes 1

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 Cysteine at codon 533 of the RYR1 protein, p.(Arg533Cys). This variant is not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in an individual with a personal or family history of an MH episode and 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_Supporting (PMID:12709367). 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). This variant segregates with MHS in 8 individuals PP1_Strong (PMID:12709367). A REVEL score >0.85 supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as Pathogenic. Criteria implemented: PS4_Supporting, PS3_Moderate, PM1, PP1_Strong, PP3_Moderate.

Met criteria codes

PM1	✔	Located in RYR1 N-terminal hotspot.
PS3_Moderate	✔	Reduced EC50 in HEK293 assay for 4-CmC
PS4_Supporting	✔	MH event during surgery, positive IVCT
PP1_Strong	✔	Eight IVCT positive mutation positive relatives.
PP3_Moderate	✔	>0.85 REVEL

Not Met criteria codes

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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