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Variant: NM_000540.3(RYR1):c.6502G>A (p.Val2168Met)

Version: 1.0

CA024603

12976 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: ba9df0d1-d974-42fd-9d62-e1fe3355bb7c
Approved on: 2022/3/29
Published on: 2022/3/29

HGVS expressions

NM_000540.3:c.6502G>A
NM_000540.3(RYR1):c.6502G>A (p.Val2168Met)
NC_000019.10:g.38494579G>A
CM000681.2:g.38494579G>A
NC_000019.9:g.38985219G>A
CM000681.1:g.38985219G>A
NC_000019.8:g.43677059G>A
NG_008866.1:g.65880G>A
ENST00000599547.6:c.6502G>A
ENST00000359596.8:c.6502G>A
ENST00000355481.8:c.6502G>A
ENST00000359596.7:c.6502G>A
ENST00000360985.7:c.6499G>A
NM_000540.2:c.6502G>A
NM_001042723.1:c.6502G>A
NM_001042723.2:c.6502G>A

Pathogenic

Met criteria codes 5

PM1 PS3_Moderate PS4 PP1_Strong PP3_Moderate

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 Valine with Methionine at codon 2168 of the RYR1 protein, p.(Val2168Met). This variant is not present in a large population database (gnomAD) at the time this variant was interpreted. This variant

has been reported in over 25 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, over 25 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:11668625; PMID:30236257; PMID:20681998 and others). Functional studies in human myotubes from nine individuals (5 families) showed an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:15299003). 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 eight individuals PP1_Strong (PMID:12434264, PMID:11575529). A REVEL score >0.85 (0.896)supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as Pathogenic. Criteria implemented: PS3_Moderate, PS4, PM1, PP1_Strong, PP3_Moderate.

Met criteria codes

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 human myotubes from nine individuals (5 families) showed an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID:15299003).
PS4	✔	This variant is not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in over 25 unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, over 25 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:11668625; PMID:30236257; PMID:20681998 and others).
PP1_Strong	✔	This variant segregates with MHS eight individuals PP1_Strong (PMID:12434264, PMID:11575529).
PP3_Moderate	✔	A REVEL score >0.85 (0.896)supports a pathogenic status for this variant, PP3_Moderate.

Curation History

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