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Variant: NM_000540.2(RYR1):c.467G>A (p.Arg156Lys)

Version: 1.1

CA024453

133133 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: bacb7f66-04ac-4528-9f35-1e061b95ec1d
Approved on: 2023/4/6
Published on: 2023/4/6

HGVS expressions

NM_000540.2:c.467G>A
NM_000540.2(RYR1):c.467G>A (p.Arg156Lys)
NC_000019.10:g.38444191G>A
CM000681.2:g.38444191G>A
NC_000019.9:g.38934831G>A
CM000681.1:g.38934831G>A
NC_000019.8:g.43626671G>A
NG_008866.1:g.15492G>A
ENST00000599547.6:c.467G>A
ENST00000359596.8:c.467G>A
ENST00000355481.8:c.467G>A
ENST00000359596.7:c.467G>A
ENST00000360985.7:c.467G>A
NM_001042723.1:c.467G>A
NM_000540.3:c.467G>A
NM_001042723.2:c.467G>A

Uncertain Significance

Met criteria codes 2

PP3_Moderate PM1

Not Met criteria codes 4

BA1 BS1 BP4 PS4

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 lysine at codon 156 of the RYR1 protein, p.

(Arg156Lys). This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in individuals with a personal or family history of an MH episode or central core disease but without sufficient information to consider the reports for informing PS4 (PMID:16835904). No functional studies were identified for this variant. 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 (0.886) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as a Variant of Unknown Significance. Criteria implemented: PM1, PP3_Moderate.

Met criteria codes

PP3_Moderate	✔	A REVEL score >0.85 (0.886) supports a pathogenic status for this variant, PP3_Moderate.
PM1	✔	This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).

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
PS4	✖	This variant has been reported in individuals with a personal or family history of an MH episode or central core disease but without sufficient information to consider the reports for informing PS4 (PMID:16835904, PMID:16917943).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000540.2(RYR1):c.467G>A (p.Arg1...	Uncertain Significance	Malignant Hyperthermia, Susceptibility To, 1	2023-04-06	1.1	-	RYR1
View	NM_000540.2(RYR1):c.467G>A (p.Arg1...	Uncertain Significance	Malignant Hyperthermia, Susceptibility To, 1	2021-03-31	1.0	-	RYR1

Showing 1 to 2 of 2 rows

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