Variant: NM_001042723.2(RYR1):c.2654G>A (p.Arg885His)

Version: 1.1

CA063661

212100 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 75f6a216-0fff-441e-a01f-0c9a73ffa399
Approved on: 2023-04-06
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HGVS expressions

NM_001042723.2:c.2654G>A
NM_001042723.2(RYR1):c.2654G>A (p.Arg885His)
NC_000019.10:g.38463499G>A
CM000681.2:g.38463499G>A
NC_000019.9:g.38954139G>A
CM000681.1:g.38954139G>A
NC_000019.8:g.43645979G>A
NG_008866.1:g.34800G>A
ENST00000599547.6:c.2654G>A
ENST00000359596.8:c.2654G>A
ENST00000355481.8:c.2654G>A
ENST00000359596.7:c.2654G>A
ENST00000360985.7:c.2654G>A
NM_000540.2:c.2654G>A
NM_001042723.1:c.2654G>A
NM_000540.3:c.2654G>A

Uncertain Significance

Not Met criteria codes 4

BP4 PS4_Supporting PP3 PM1

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 histidine at codon 885 of the RYR1 protein (p.Arg885His). The maximum allele frequency for this variant among the six major gnomAD populations is SAS: 0.00042, a frequency

consistent with pathogenicity for MHS. 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), however, the MAF in the SAS population in gnomAD does not allow PS4 to be utilized (PMID:30236257). No functional studies were identified for this variant.This variant does not reside in a hotspot for pathogenic variants that contribute to MHS. A REVEL score of 0.609 supports neither a pathogenic nor a benign status for this variant. This variant has been classified as a Variant of Unknown Significance. Criteria implemented: none.

Not Met criteria codes

BP4	✖	A REVEL score of 0.609 supports neither a pathogenic nor a benign status for this variant.
PS4_Supporting	✖	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), however, the MAF in the SAS population in gnomAD does not allow PS4 to be utilized (PMID:30236257).
PP3	✖	A REVEL score of 0.609 supports neither a pathogenic nor a benign status for this variant.
PM1	✖	This variant does not reside in a hotspot for pathogenic variants that contribute to MHS.

Curation History

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