Variant: NM_000540.2(RYR1):c.10097G>A (p.Arg3366His)

Version: 2.0

CA023812

132990 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 9fc90212-f5da-4a79-b8a1-355b92454a8f
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HGVS expressions

NM_000540.2:c.10097G>A
NM_000540.2(RYR1):c.10097G>A (p.Arg3366His)
NC_000019.10:g.38519292G>A
CM000681.2:g.38519292G>A
NC_000019.9:g.39009932G>A
CM000681.1:g.39009932G>A
NC_000019.8:g.43701772G>A
NG_008866.1:g.90593G>A
ENST00000599547.6:c.10036G>A
ENST00000359596.8:c.10097G>A
ENST00000355481.8:c.10097G>A
ENST00000359596.7:c.10097G>A
ENST00000360985.7:c.10094G>A
ENST00000594335.5:c.3499G>A
ENST00000599547.5:c.904G>A
NM_001042723.1:c.10097G>A
NM_000540.3:c.10097G>A
NM_001042723.2:c.10097G>A

Likely Benign

Met criteria codes 1

BS1

Not Met criteria codes 4

PS4 PP3 PM1 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 histidine at codon 3366 of the RYR1 protein, p.(Arg3366His). The maximum allele frequency for this variant among the six major gnomAD populations is NFE: 0.00135, this is considered to be more common than expected for a pathogenic variant causing autosomal dominantly inherited MHS, BS1. This variant has been reported in four unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, all 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) (PMID: 25958340, 25658027, 25735680). However, the high MAF in the NFE population in gnomAD precludes the use of PS4. 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 0.68 supports neither a pathogenic nor a benign status for this variant. This variant has been classified as Likely Benign. Criteria implemented: BS1.

Met criteria codes

BS1	✔	The maximum allele frequency for this variant among the six major gnomAD populations is NFE: 0.00135, this is considered to be more common than expected for a pathogenic variant causing autosomal dominantly inherited MHS, BS1.

Not Met criteria codes

PS4	✖	This variant has been reported in four unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, all 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) (PMID: 25958340, 25658027, 25735680). However, the high MAF in the NFE population in gnomAD precludes the use of PS4.
PP3	✖	A REVEL score of 0.68 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.
BP4	✖	A REVEL score of 0.68 supports neither a pathogenic nor a benign status for this variant.

Curation History

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