

Variant: *NM_001042723.2:c.1024G>A*

Version: 2.0

CA405682843 [↗](#)

1214000 (ClinVar) [↗](#)

Gene: RYR1 ([HGNC:6261](#))

Condition: malignant hyperthermia, susceptibility to, 1 ([MONDO:0007783](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: cccb11b6-df8a-4412-8b02-f335d64a548b

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HGVS expressions

NM_001042723.2:c.1024G>A

NC_000019.10:g.38448715G>A

CM000681.2:g.38448715G>A

NC_000019.9:g.38939355G>A

CM000681.1:g.38939355G>A

NC_000019.8:g.43631195G>A

NG_008866.1:g.20016G>A

ENST00000599547.6:c.1024G>A

ENST00000359596.8:c.1024G>A

ENST00000355481.8:c.1024G>A

ENST00000359596.7:c.1024G>A

ENST00000360985.7:c.1024G>A

NM_000540.2:c.1024G>A

NM_001042723.1:c.1024G>A

NM_000540.3:c.1024G>A

Likely Pathogenic

Met criteria codes 4

PS3_Moderate

PP3_Moderate

PM1

PS4_Supporting

Not Met criteria codes 2

BS1

BA1

Evidence Links 0

Expert Panel

[Malignant Hyperthermia Susceptibility VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen Malignant Hyperthermia Susceptibility Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RYR1 Version 2*

[↗](#) **Criteria Specification Approval History**

[↗](#) **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 glutamic acid with lysine at codon 342 of the RYR1 protein, p.(Glu342Lys). This variant was 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:24433488). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID: 39890490). 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 (0.927) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as a Variant of Likely Pathogenic. Criteria implemented: PS3_Moderate, PS4_Supporting, PM1, PP3_Moderate.

Met criteria codes

PS3_Moderate			Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists, PS3_Moderate (PMID: 39890490).
PP3_Moderate			A REVEL score >0.85 (0.927) 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).
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), PS4_Supporting (PMID:24433488).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History



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