The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000540.2(RYR1):c.1615T>C (p.Phe539Leu)

Version: 1.1

CA024297

133104 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1f83c96d-f6ca-4543-aeaa-420f85809094
Approved on: 2023/4/6
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HGVS expressions

NM_000540.2(RYR1):c.1615T>C (p.Phe539Leu)
NM_000540.2:c.1615T>C
NC_000019.10:g.38455489T>C
CM000681.2:g.38455489T>C
NC_000019.9:g.38946129T>C
CM000681.1:g.38946129T>C
NC_000019.8:g.43637969T>C
NG_008866.1:g.26790T>C
ENST00000599547.6:c.1615T>C
ENST00000359596.8:c.1615T>C
ENST00000355481.8:c.1615T>C
ENST00000359596.7:c.1615T>C
ENST00000360985.7:c.1615T>C
NM_001042723.1:c.1615T>C
NM_000540.3:c.1615T>C
NM_001042723.2:c.1615T>C

Likely Pathogenic

Met criteria codes 4

PP1 PM1 PP3_Moderate PS4_Moderate

Not Met criteria codes 3

BA1 BS1 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 phenylalanine with leucine at codon 539 of the RYR1 protein, p.Phe539Leu. This variant was not present in a large population database (gnomAD) at the time this variant was interpreted. This variant has been reported in three individuals with a personal or family history of an MH episode, 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), PS4_Moderate (PMID:30236257, PMID:18564801 (reported two individuals, may be related with shared haplotype)). This variant segregates with MHS with three informative meiosis, PP1_Supporting (PMID:18564801). 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 (0.934) supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as a Variant of Unknown Significance. Criteria implemented: PS4_Moderate, PM1, PP1_Supporting, PP3_Moderate.

Met criteria codes

PP1	✔	This variant segregates with MHS with three informative meiosis, PP1_Supporting (PMID:18564801).
PM1	✔	This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).
PP3_Moderate	✔	A REVEL score >0.85 (0.934) supports a pathogenic status for this variant, PP3_Moderate.
PS4_Moderate	✔	This variant has been reported in three individuals with a personal or family history of an MH episode, 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), PS4_Moderate (PMID:30236257, PMID:18564801 (reported two individuals, may be related with shared haplotype)).

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

Curation History

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