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Variant: NM_000540.3(RYR1):c.103T>C (p.Cys35Arg)

Version: 1.0

CA023838

132995 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8410e5b5-ba69-4c4b-a83f-f2bbb062586d
Approved on: 2021/3/18
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HGVS expressions

NM_000540.3(RYR1):c.103T>C (p.Cys35Arg)
NM_000540.3:c.103T>C
NC_000019.10:g.38440802T>C
CM000681.2:g.38440802T>C
NC_000019.9:g.38931442T>C
CM000681.1:g.38931442T>C
NC_000019.8:g.43623282T>C
NG_008866.1:g.12103T>C
ENST00000599547.6:c.103T>C
ENST00000359596.8:c.103T>C
ENST00000355481.8:c.103T>C
ENST00000359596.7:c.103T>C
ENST00000360985.7:c.103T>C
NM_000540.2:c.103T>C
NM_001042723.1:c.103T>C
NM_001042723.2:c.103T>C

Pathogenic

Met criteria codes 4

PP3_Moderate PS4_Moderate PM1 PP1_Strong

Not Met criteria codes 5

PS3 BA1 BS1 BS3 BP4

Evidence Links 2

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 cysteine with arginine at codon 35 of the RYR1 protein, p.(Cys35Arg). The maximum allele frequency for this variant among the six major gnomAD populations is NFE: 0.000009, a frequency consistent with pathogenicity for MHS. This variant has been reported in three unrelated individuals who have a personal or family history of a malignant hyperthermia reaction and positive in vitro contracture test (IVCT) or caffeine halothane contracture test (CHCT) result (when the proband was unavailable for testing a positive diagnostic test result in a mutation positive relative was counted), PS4_Moderate (PMID:17710899, PMID:20681998, PMID:9066328). Functional studies in HEK293 cells show conflicting data regarding sensitivity to RYR1 agonists, PS3/BS3 were not implemented (PMID:9334205, PMID:26115329). This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704). This variant segregates with MHS in 11 individuals, PP1_Strong (PMID:9066328). A REVEL score > 0.85 supports pathogenicity, PP3_Moderate. Criteria implemented: PS4_Moderate, PM1, PP3_Moderate, PP1_Strong. Based on using Bayes to combine criteria this variant is assessed as Pathogenic, (PMID: 29300386).

Met criteria codes

PP3_Moderate	✔	REVEL 0.947
PS4_Moderate	✔	Three unrelated cases with history of MH event (personal/family history) and a positive IVCT.
PM1	✔	In N-terminal RYR1 hotspot.
PP1_Strong	✔	Eleven co-segregation events.

Not Met criteria codes

PS3	✖	Conflicting data. Variant showed reduced EC50 compared to WT for halothane but not for caffeine. PubMed:9334205 Variant did not show significant lowered EC50 as compared to WT construct. PubMed:26115329
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
BS3	✖	Conflicting data. Variant showed reduced EC50 compared to WT for halothane but not for caffeine. PubMed:9334205 Variant did not show significant lowered EC50 as compared to WT construct. PubMed:26115329
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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