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Variant: NM_000540.3(RYR1):c.1565A>C (p.Tyr522Ser)

Version: 1.0

CA024286

12993 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: malignant hyperthermia, susceptibility to, 1 (MONDO:0007783)
Inheritance Mode: Autosomal dominant inheritance
UUID: 3dabd68e-7090-43d8-9cbb-77ae98ef977d
Approved on: 2021/3/18
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HGVS expressions

NM_000540.3(RYR1):c.1565A>C (p.Tyr522Ser)
NM_000540.3:c.1565A>C
NC_000019.10:g.38455359A>C
CM000681.2:g.38455359A>C
NC_000019.9:g.38945999A>C
CM000681.1:g.38945999A>C
NC_000019.8:g.43637839A>C
NG_008866.1:g.26660A>C
ENST00000599547.6:c.1565A>C
ENST00000359596.8:c.1565A>C
ENST00000355481.8:c.1565A>C
ENST00000359596.7:c.1565A>C
ENST00000360985.7:c.1565A>C
NM_000540.2:c.1565A>C
NM_001042723.1:c.1565A>C
NM_001042723.2:c.1565A>C

Pathogenic

Met criteria codes 5

PS4_Supporting PP1 PM1 PS3 PP3_Moderate

Not Met criteria codes 2

BA1 BS1

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 tyrosine with serine at codon 522 of the RYR1 protein, p.(Tyr522Ser). The maximum allele frequency for this variant among the six major gnomAD populations is EAS: 0.00005, a frequency consistent with pathogenicity for MHS. This variant has been reported in two unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, one 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_Supporting (PMID:7829078, PMID:19020143). Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists. A knock-in mouse model supports pathogenicity of this variant demonstrating a malignant hyperthermia reaction in response to agonist, as well ex vivo studies showed increased response to agonist with increased calcium release, PS3 (PMID:31607937, PMID:9334205).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 three individuals, PP1 (PMID:7829078). A REVEL score >0.85 supports a pathogenic status for this variant, PP3_Moderate. This variant has been classified as Pathogenic. Criteria implemented: PS4_Supporting, PS3, PM1, PP1, PP3_Moderate.

Met criteria codes

PS4_Supporting	✔	This variant has been reported in two unrelated individuals who have a personal or family history of a malignant hyperthermia reaction, one 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_Supporting (PMID:7829078, PMID:19020143).
PP1	✔	This variant segregates with MHS in three individuals, PP1_Supporting (PMID:7829078).
PM1	✔	This variant resides in a region of RYR1 considered to be a hotspot for pathogenic variants that contribute to MHS, PM1 (PMID: 21118704).
PS3	✔	Functional studies in HEK293 cells show an increased sensitivity to RYR1 agonists. A knock-in mouse model supports pathogenicity of this variant demonstrating a malignant hyperthermia reaction in response to agonist, as well ex vivo studies showed increased response to agonist with increased calcium release, PS3_Strong (PMID:31607937, PMID:9334205).
PP3_Moderate	✔	REVEL > 0.85

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

Curation History

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