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Variant: NM_000540.3(RYR1):c.10204T>G (p.Cys3402Gly)

Version: 1.0

CA023822

42098 (ClinVar)

Gene: RYR1 (HGNC:6261)
Condition: RYR1-related myopathy (MONDO:0100150)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7b52166b-8d2a-4c9f-b5e9-f39c4eca57b6
Approved on: 2025/2/10
Published on: 2025/4/3

HGVS expressions

NM_000540.3(RYR1):c.10204T>G (p.Cys3402Gly)
NM_000540.3:c.10204T>G
NC_000019.10:g.38519399T>G
CM000681.2:g.38519399T>G
NC_000019.9:g.39010039T>G
CM000681.1:g.39010039T>G
NC_000019.8:g.43701879T>G
NG_008866.1:g.90700T>G
ENST00000599547.6:c.10143T>G
ENST00000359596.8:c.10204T>G
ENST00000355481.8:c.10204T>G
ENST00000359596.7:c.10204T>G
ENST00000360985.7:c.10201T>G
ENST00000594335.5:c.3606T>G
ENST00000599547.5:c.1011T>G
NM_000540.2:c.10204T>G
NM_001042723.1:c.10204T>G
NM_001042723.2:c.10204T>G

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP1 | PP3

Not Met criteria codes 23

PVS1 | PM1 | PM5 | PM4 | PM6 | PM2 | BA1 | BS2 | BS1 | BS4 | BS3 | BP4 | BP3 | BP1 | BP2 | BP5 | BP7 | PS1 | PS2 | PS3 | PS4 | PP2 | PP4

Evidence Links 0

Expert Panel

Congenital Myopathies VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RYR1 Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_000540.3:c.10204T>G (p.Cys3402Gly) variant in RYR1 is a missense variant predicted to cause a substitution of cysteine by glycine at amino acid 3402. The computational predictor REVEL gives a score of 0.851, which is above the threshold for predicting a damaging effect on RYR1 variants (PP3). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00006 (7/117872 alleles) in European (non-Finnish) population, which is higher than the ClinGen Congenital Myopathies VCEP threshold (≤0.00000697) for PM2_Supporting and lower than ClinGen Congenital Myopathies VCEP threshold (≥0.000697) for BS1, therefore no population criteria can be applied. The variant has been reported in trans with a second pathogenic RYR1 variant or a rare variant of uncertain significance in RYR1 in 10 probands with clinical features of congenital myopathy (PMID: 20583297; Synnovis internal data SCV001468505.1; Invitae internal data SCV000659742.9) (PM3_Very Strong). The variant along with another pathogenic variant in trans was identified in two siblings with congenital myopathy suggesting cosegregation (Invitae internal data) (PP1). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive RYR1-related myopathy based on the ACMG/AMP criteria applied as specified by the ClinGen Congenital Myopathy VCEP: PM3_Very Strong, PP1, PP3 (ClinGen Congenital Myopathies VCEP Specifications 2.0.0; 2/10/2025).

Met criteria codes

PM3_Very Strong	✔	The variant has been reported in trans with a second pathogenic RYR1 variant or a rare variant of uncertain significance in RYR1 in 10 probands with clinical features of congenital myopathy (PMID: 20583297; Synnovis internal data SCV001468505.1; Invitae internal data SCV000659742.9). Total points per the PM3 chart from laboratory data and Patient 2 of PMID: 20583297 using submissions from Clinvar is 7 points. Even when very conservatively calling L/LP variants in ClinVar without VCEP classifications as VUSs, the proband counting would be 4 points which is also over PM3_Very Strong threshold.
PP1	✔	Labcorp Genetics reported 2 affected siblings found to have this variant confirmed in trans with another RYR1 variant by parental testing.
PP3	✔	The REVEL score is over 0.7

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	The variant is not within the pore/transmembrane region of RYR1 critical for protein function (amino acids 4800-4950)
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	The variant was inherited from heterozygous parent in PMID:20583297
PM2	✖	Variant is present in 7 heterozygotes in gnomAD and 2 heterozygotes in ExAC and has an allele frequency of 0.00003 which is above the PM2 frequency threshold for both autosomal recessive and autosomal dominant variants

BA1	ℹ	✖	Variant is present in 7 heterozygotes in gnomAD and 2 heterozygotes in ExAC and has an allele frequency of 0.00003 which is less than the BA1 frequency threshold
BS2	ℹ	✖	No homozygotes noted in population databases nor in affected patients.
BS1	ℹ	✖	Variant is present in 7 heterozygotes in gnomAD and 2 heterozygotes in ExAC and has an allele frequency of 0.00003 which is less than the BS1 frequency threshold (≥0.000697) for both autosomal recessive but above the ≥0.00000486 threshold for autosomal dominant.
BS4	ℹ	✖	No available segregation data
BS3		✖	No functional data
BP4	ℹ	✖	The REVEL score is over 0.7
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	ℹ	✖	Heterozygous parent for other variant was unaffected.
BP5	ℹ	✖	PMID: 20583297 had negative genetic testing for DM1 and myotubular myopathy.
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	ℹ	✖	The variant was inherited from heterozygous parent in PMID:20583297
PS3	ℹ	✖	No functional data
PS4		✖	Not applicable for autosomal recessive RYR1
PP2		✖	RYR1 is not constrained for missense variants
PP4	ℹ	✖	The proband in PMID: 20583297 only meets the ophthalmoplegia specification outlined in the VCEP's PP4 criteria specifications, therefore, PP4 is not met.

Curation History

Showing 1 to 1 of 1 rows

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