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Variant: NM_213599.3(ANO5):c.172C>T (p.Arg58Trp)

Version: 1.1

CA202865

197402 (ClinVar)

Gene: ANO5 (HGNC:203859)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 05785e65-0fb1-4b7f-85d7-691efc434976
Approved on: 2025/6/24
Published on: 2025/7/8

HGVS expressions

NM_213599.3:c.172C>T
NM_213599.3(ANO5):c.172C>T (p.Arg58Trp)
NC_000011.10:g.22218279C>T
CM000673.2:g.22218279C>T
NC_000011.9:g.22239825C>T
CM000673.1:g.22239825C>T
NC_000011.8:g.22196401C>T
NG_015844.1:g.30104C>T
ENST00000682084.1:n.3346C>T
ENST00000682266.1:c.-270-2818C>T
ENST00000682341.1:c.139-2818C>T
ENST00000682530.1:c.136-464C>T
ENST00000682684.1:n.560-2818C>T
ENST00000683197.1:c.139-2818C>T
ENST00000683411.1:c.-270-2818C>T
ENST00000683437.1:c.-270-2818C>T
ENST00000683834.1:n.381-2818C>T
ENST00000683897.1:n.425-2818C>T
ENST00000684365.1:n.550-2818C>T
ENST00000684663.1:c.136-2818C>T
ENST00000324559.9:c.172C>T
ENST00000648804.1:n.670-307C>T
ENST00000324559.8:c.172C>T
NM_001142649.1:c.169C>T
NM_213599.2:c.172C>T
NM_001142649.2:c.169C>T

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP1 | PP4

Not Met criteria codes 4

PM2 | PM5 | BS1 | PP3

Evidence Links 0

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ANO5 Version 1.0.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.172C>T variant in ANO5 is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 58 (p.Arg58Trp). This variant has been detected in at least seven individuals with limb girdle muscular dystrophy or persistent hyperCKemia, including in unknown phase with a pathogenic variant (c.191dup x2, 1.0 pts, PMID: 22499103, 30564623, LOVD Individual #00220701) and confirmed in trans with a pathogenic variant (c.2018A>G p.(Tyr673Cys), 1.0 pt, PMID: 23055322; c.148C>T p.(Arg50Ter), 1.0 pt, PMID: 30564623, LOVD Individual #00078872). Three individuals were homozygous for the variant, all of whom experienced progressive muscle weakness or showed myopathic or dystrophic signs on muscle biopsy (1.0 pt, PMID: 31353849, 27854218) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness (PP4). The variant has also been reported to segregate with autosomal recessive LGMD in one affected family member (PP1; PMID: 23055322). The Grpmax filtering allele frequency for this variant is 0.002728 in gnomAD v4.1.0 exomes (the lower bound of the 95% confidence interval of 23/5762 Middle Eastern chromosomes), which is higher than the threshold of 0.001 for BS1. The Middle Eastern genetic ancestry group also includes three homozygous individuals. However, in light of the overall evidence for this variant and the potential for late onset and subclinical presentation, the LGMD VCEP considers this variant a BS1 exception. The computational predictor REVEL gives a score of 0.572 (PP3, BP4 not met). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (LGMD VCEP specifications version 1.0.0; 06/24/2025): PM3_Very Strong, PP4, PP1.

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in at least seven individuals with limb girdle muscular dystrophy or persistent hyperCKemia, including in unknown phase with a pathogenic variant (c.191dup x2, 1.0 pts, PMID: 22499103, 30564623; LOVD Individual #00220701) and confirmed in trans with a pathogenic variant (c.2018A>G p.(Tyr673Cys), 1.0 pt, PMID: 23055322; c.148C>T p.(Arg50Ter), 1.0 pt, PMID: 30564623; LOVD Individual #00078872). Three individuals were homozygous for the variant (1.0 pt, PMID: 31353849, 27854218) (PM3_Very Strong).
PP1	✔	The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in one affected family member (PP1; PMID: 23055322).
PP4	✔	At least one patient with this variant displayed progressive muscle weakness, which is highly specific for autosomal recessive limb-girdle muscular dystrophy (PP4, PMID:32925086).

Not Met criteria codes

PM2	✖	The highest maximum allele frequency for this variant is 0.0004356 (15/34438 exome chromosomes) in the Admixed American population in gnomAD v2.1.1, which exceeds the LGMD VCEP threshold for PM2_Supporting (<0.0001) (criterion not met).
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1		✖	The Grpmax filtering allele frequency for this variant is 0.002728 in gnomAD v4.1.0 exomes (the lower bound of the 95% confidence interval of 23/5762 Middle Eastern chromosomes), which is higher than the threshold of 0.001 for BS1. The Middle Eastern genetic ancestry group also includes three homozygous individuals. In light of the overall evidence for this variant and the potential for late onset and subclinical disease, the LGMD VCEP considers this variant a BS1 exception. Approved as BS1 exception on 06/25/2025 based on gnomAD v4 data and evidence summary updated
PP3		✖	The computational predictor REVEL gives a score of 0.572 (PP3, BP4 not met).

Curation History

Showing 1 to 2 of 2 rows

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