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Variant: NM_213599.3(ANO5):c.1450C>T (p.Arg484Cys)

Version: 1.0

CA5923264

289098 (ClinVar)

Gene: ANO5 (HGNC:203859)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 69a6766c-2bdd-4588-b3fe-932be6ebc89f
Approved on: 2026/4/29
Published on: 2026/5/7

HGVS expressions

NM_213599.3:c.1450C>T
NM_213599.3(ANO5):c.1450C>T (p.Arg484Cys)
NC_000011.10:g.22259561C>T
CM000673.2:g.22259561C>T
NC_000011.9:g.22281107C>T
CM000673.1:g.22281107C>T
NC_000011.8:g.22237683C>T
NG_015844.1:g.71386C>T
ENST00000682266.1:c.1000C>T
ENST00000682341.1:c.1408C>T
ENST00000683197.1:c.1408C>T
ENST00000683411.1:c.1000C>T
ENST00000683437.1:c.1000C>T
ENST00000683613.1:n.2444C>T
ENST00000684663.1:c.1405C>T
ENST00000324559.9:c.1450C>T
ENST00000648804.1:n.1785C>T
ENST00000324559.8:c.1450C>T
NM_001142649.1:c.1447C>T
NM_213599.2:c.1450C>T
NM_001142649.2:c.1447C>T

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PM3_Strong PP4

Not Met criteria codes 4

PS1 PS3 PM5 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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.1450C>T variant in ANO5 is a missense variant expected to cause the substitution of arginine at amino acid position 484 with cysteine, p.(Arg484Cys). This variant has been reported in at least three individuals with features consistent with LGMD (PMID: 30564623, 34264321; GRASP-LGMD Consortium, ClinVar SCV001954366.1 internal data communication), including in unconfirmed phase with a pathogenic variant in two patients (c.191dup (p.Asn64LysfsTer15, 0.5 pts, GRASP-LGMD Consortium internal data communication; c.304_308del p.(Lys102ValfsTer2), 0.5 pts, PMID: 34264321) and confirmed in trans with a pathogenic variant in one patient (c.1898+1G>A, 1.0 pt, ClinVar SCV001954366.1 internal data communication) (PM3_Strong). At least one of these patients presented with progressive limb girdle muscle weakness (PP4). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000019574 (15/1180006 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold of 0.0001, meeting the criteria for PM2_Supporting. The computational predictor REVEL also gives a score of 0.689, which is below the threshold of 0.7 (PP3 not met). Another nucleotide change resulting in the same amino acid change, c.1450C>A p.(Arg484Ser), has also been reported in association with LGMD (PMID: 36913258). In summary, this variant meets the criteria to be classified as Likely pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the LGMD VCEP (specifications v2.0.0; 04/29/2026): PM3_Strong, PP4, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000019574 (15/1180006 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold of 0.0001, meeting the criteria for PM2_Supporting.
PM3_Strong	✔	The NM_213599.3: c.1450C>T variant in ANO5 is a missense variant expected to cause the substitution of arginine at amino acid position 484 with cysteine, p.(Arg484Cys). This variant has been reported in at least three individuals with features consistent with LGMD (PMID: 30564623, 34264321; GRASP-LGMD Consortium, ClinVar SCV001954366.1 internal data communication), including in unconfirmed phase with a pathogenic variant in two patients (c.191dup (p.Asn64LysfsTer15, 0.5 pts, GRASP-LGMD Consortium internal data communication; c.304_308del p.(Lys102ValfsTer2), 0.5 pts, PMID: 34264321) and confirmed in trans with a pathogenic variant in one patient (c.1898+1G>A, 1.0 pt, ClinVar SCV001954366.1 internal data communication) (PM3_Strong).
PP4	✔	At least one of these patients presented with progressive limb girdle muscle weakness (PP4).

Not Met criteria codes

PS1	✖	Another nucleotide change resulting in the same amino acid change, c.1450C>A p.(Arg484Ser), has been reported in association with LGMD (PMID: 36913258), but this nucleotide change also has insufficient evidence to be classified above VUS. CA379922056 not in ClinVar or LOVD reported in unconfirmed phase with c.191dupA p.Asn64Lysfs*15 in PMID: 36913258 de Bruyn et al. (2023). Inclusion criteria: (i) genetically confirmed diagnosis of ANO5-related muscle disease by identification of two heterozygous or one homozygous pathogenic or probably pathogenic variant or VUS in the ANO5 gene; and (ii) sufficient data available in the medical files concerning clinical symptoms at onset and clinical evolution over time, ambulation status and use of walking aids, and presence of cardiac and respiratory symptoms. Patients were categorized according to the clinical phenotype at the individual patient level (thus not at the family level) in four groups: LGMD-R12 (predominant proximal weakness or combined proximal and distal weakness in lower and/or upper extremities), MMD3 (predominant distal weakness in lower and/or upper extremities), pseudometabolic myopathy [persistently elevated serum creatine kinase (CK) levels associated with exercise intolerance and/ or myalgia without significant muscle weakness on neurological

examination] or asymptomatic hyperCKaemia (persistently elevated serum-CK levels in the absence of weakness or other symptoms, but clinical signs without patient complaints may be present). (PM3_Supporting, PP4) absent from gnomAD v4 (PM2_Supporting) REVEL 0.695 (PP3 not met)

PS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Per specs, the REVEL score for the missense variant under curation should be >0.7, but the score for this variant is 0.689, so PM5 is not applicable c.1451G>A (p.Arg484His) LP in ClinVar by Labcorp-Invitae, seemingly based on PM5 not in LOVD PMID: 36913258 de Bruyn et al. (2023): 1 homozygote, no reported consanguinity (PP4, PM3_Supporting) 5 alleles in gnomAD v4 (PM2_Supporting) REVEL: 0.777 (PP3) c.1450C>A p.(Arg484Ser) PMID: 34550615, 34145687
PP3	✖	The computational predictor REVEL also gives a score of 0.689, which is below the threshold of 0.7 (PP3 not met). SpliceAI: 0.0900

Curation History

Showing 1 to 1 of 1 rows

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