

Variant: *NM_213599.3(ANO5):c.751C>T (p.Pro251Ser)*

Version: 1.0

CA379920329 [↗](#)

1488412 (ClinVar) [↗](#)

Gene: ANO5 ([HGNC:203859](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: a4849de3-cf27-4d8d-b704-f2b9d0780db7

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HGVS expressions

NM_213599.3(ANO5):c.751C>T (p.Pro251Ser)

NM_213599.3:c.751C>T

NC_000011.10:g.22236265C>T

CM000673.2:g.22236265C>T

NC_000011.9:g.22257811C>T

CM000673.1:g.22257811C>T

NC_000011.8:g.22214387C>T

NG_015844.1:g.48090C>T

ENST00000682266.1:c.301C>T

ENST00000682341.1:c.709C>T

ENST00000682530.1:c.*683C>T

ENST00000682684.1:n.1130C>T

ENST00000683197.1:c.709C>T

ENST00000683411.1:c.301C>T

ENST00000683437.1:c.301C>T

ENST00000683613.1:n.1745C>T

ENST00000683834.1:n.951C>T

ENST00000684663.1:c.706C>T

ENST00000324559.9:c.751C>T

ENST00000648804.1:n.1213+8679C>T

ENST00000324559.8:c.751C>T

NM_001142649.1:c.748C>T

NM_213599.2:c.751C>T

NM_001142649.2:c.748C>T

Uncertain Significance

Met criteria codes **4**

PM3_Supporting

PM2_Supporting

PP3

PP4

Not Met criteria codes **1**

PM5

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**

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.751G>T variant in ANO5 is a missense variant expected to cause the substitution of proline with serine at position 251, p.(Pro251Ser). This variant has been reported in one individual with a clinical suspicion of LGMD, where it was identified in unconfirmed phase with a pathogenic variant (c.108_109del p.(Glu36AspfsTer7), 0.5 pts, PMID: 37688281) (PM3_Supporting, PP4). This variant is absent from gnomAD v4.1.0 in a region with good sequencing coverage (PM2_Supporting). The computational predictor REVEL gives a score of 0.75, which exceeds the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3). In summary, there is currently insufficient evidence to classify this variant as pathogenic or benign, and it remains a variant of uncertain significance 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 2.0.0; 03/13/2026): PM3_Supporting, PP4, PM2_Supporting, PP3.

Met criteria codes

PM3_Supporting			This variant has been reported in one individual with a clinical suspicion of LGMD, where it was identified in unconfirmed phase with a pathogenic variant (c.108_109del p.(Glu36AspfsTer7), 0.5 pts, PMID: 37688281) (PM3_Supporting). ClinVar: VUS by Revvity (SCV003826762.3) - this almost certainly reflects the Nallamilli (2023)/GRASP case included above VUS by LabCorp (formerly Invitae) (SCV002274573.4, last evaluated April 2024) not in LOVD no additional literature identified To upgrade to LP, PM3 would need to reach _Strong, meaning 1.5 more PM3 pts are needed. It seems extremely unlikely that LabCorp (formerly Invitae) would have multiple cases, particularly with a VUS classification in 2024, and so we chose not to reach out for their internal data at this time.
PM2_Supporting			This variant is absent from gnomAD v4.1.0 in a region with good sequencing coverage (PM2_Supporting).
PP3			The computational predictor REVEL gives a score of 0.75, which exceeds the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3). highest masked SpliceAI delta score: 0.11
PP4			This variant has been identified in a heterozygous state with a second presumed diagnostic ANO5 variant in one individual with a clinical suspicion of LGMD (PMID: 37688281; PP4).

Not Met criteria codes

PM5			c.752C>T p.(Pro251Leu) has been reported (PMID: 35563815 - unconfirmed phase with c.41-1G>A, which is P by the VCEP). However, that appears to be the only literature report, and the variant is not in LOVD or ClinVar, suggesting it will not reach an LP classification (PP3, PM2_Supporting, PM3_Supporting, PP4).
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