

Variant: *NM_213599.3(ANO5):c.242A>G (p.Asp81Gly)*

Version: 1.0

CA224411 [↗](#)

96679 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: db6797b3-b077-422c-9623-a5443a6e0d3a

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HGVS expressions

NM_213599.3(ANO5):c.242A>G (p.Asp81Gly)

NM_213599.3:c.242A>G

NC_000011.10:g.22221158A>G

CM000673.2:g.22221158A>G

NC_000011.9:g.22242704A>G

CM000673.1:g.22242704A>G

NC_000011.8:g.22199280A>G

NG_015844.1:g.32983A>G

ENST00000682266.1:c.-209A>G

ENST00000682341.1:c.200A>G

ENST00000682530.1:c.*174A>G

ENST00000682684.1:n.621A>G

ENST00000683197.1:c.200A>G

ENST00000683411.1:c.-209A>G

ENST00000683437.1:c.-209A>G

ENST00000683613.1:n.1236A>G

ENST00000683834.1:n.442A>G

ENST00000683897.1:n.486A>G

ENST00000684365.1:n.611A>G

ENST00000684663.1:c.197A>G

ENST00000324559.9:c.242A>G

ENST00000648804.1:n.807A>G

ENST00000324559.8:c.242A>G

NM_001142649.1:c.239A>G

NM_213599.2:c.242A>G

NM_001142649.2:c.239A>G

Pathogenic

Met criteria codes **5**

BP2

PM3_Very Strong

PP3

PP4

PM2_Supporting

Not Met criteria codes **2**

PP1

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

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3 c.242A>G variant in ANO5 is a missense variant predicted to cause substitution of aspartic acid with glycine at codon 81, p.(Asp81Gly). This variant has been detected in at least 13 unrelated individuals with features consistent with LGMD or anoctaminopathy (PMID: 30564623, 29970176, 23047743, 22980763, 31395899, 22402862; ClinVar SCV001574736.5, SCV000582412.4 internal data communication), including in unconfirmed phase with a pathogenic variant in six unrelated cases (c.989dup p.(Leu330PhefsTer6) x2, 1.0 pt, PMID: 30564623, LOVD Individual #00220727, ClinVar SCV001574736.5 internal data communication; c.191dup p.(Asn64LysfsTer15) x2, 1.0 pt, PMID: 30564623, LOVD Individual #00221127, ClinVar SCV000582412.4 internal data communication; c.2272C>T p.(Arg758Cys) x2, 1.0 pt, PMID: 31395899, 22402862). It has also been confirmed in trans with a pathogenic variant in one patient (c.191dup p.(Asn64LysfsTer15), 1.0 pt, ClinVar SCV001574736.5 internal data communication) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness (PP4). Two affected family members of a proband with this variant and a second presumed diagnostic ANO5 allele were shown to have the same two variants, but phase was not confirmed (PMID: 22980763; PP1 not met). The filtering allele frequency for this variant is 0.00006 in gnomAD v4.1.0 (the upper bound of the 95% confidence interval of 57/1178734 European (non-Finnish) alleles), which is lower than the VCEP threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.851, which exceeds the threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3). This variant was reported in a heterozygous state in an individual with clinically suspected LGMD who was apparently homozygous for the pathogenic variant c.191dup p.(Asn64LysfsTer15), suggesting the variants occurred in cis on one allele (PMID: 30564623, LOVD Individual #00220749; BP2). However, these variants are predicted on different haplotypes in gnomAD v2.1.1, suggesting it may not be a common complex allele, and this evidence is not considered contradictory with the final classification. 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 2.0.0; 02/10/2026): PM3_Very Strong, PP4, PM2_Supporting, PP3, BP2.

Met criteria codes

BP2	 	This variant has been reported in a heterozygous state in an individual with clinically suspected LGMD who was apparently homozygous for the pathogenic variant c.191dup p.(Asn64LysfsTer15), suggesting the variants occurred in cis on one allele (PMID: 30564623, LOVD Individual #00220749; BP2). These variants are predicted on different haplotypes in gnomAD v2.1.1
PM3_Very Strong	 	This variant has been detected in at least 13 unrelated individuals with features consistent with LGMD or anoctaminopathy (PMID: 30564623, 29970176, 23047743, 22980763, 31395899, 22402862; ClinVar SCV001574736.5, SCV000582412.4 internal data communication), including in unconfirmed phase with a pathogenic variant in six unrelated cases (c.989dup p.(Leu330PhefsTer6) x2, 1.0 pt, PMID: 30564623, LOVD Individual #00220727, ClinVar SCV001574736.5 internal data communication; c.191dup p.(Asn64LysfsTer15) x2, 1.0 pt, PMID: 30564623, LOVD Individual #00221127, ClinVar SCV000582412.4 internal data communication; c.2272C>T p.(Arg758Cys) x2, 1.0 pt, PMID: 31395899, 22402862). It has also been confirmed in trans with a pathogenic variant in one patient (c.191dup p.(Asn64LysfsTer15), 1.0 pt, ClinVar SCV001574736.5 internal data communication) (PM3_Very Strong). independently P variants scored in unknown phase: c.989dup p.(Leu330PhefsTer6): predicted on different haplotypes c.191dup p.(Asn64LysfsTer15): predicted on different haplotypes c.2272C>T p.(Arg758Cys) (x2): predicted on different haplotypes to potentially curate: c.2498T>A p.(Met833Lys) (0.5 if P): predicted on different haplotypes, solidly P in ClinVar (Variation ID 285338) but PM3_Very Strong or segregation OR PM5 required for full P classification; not on our curation list c.1631-7_1631-3del (0.25 if LP but seems like VUS): not in gnomAD v2 but 2 alleles in v4, VUS by Eurofins in ClinVar (Variation ID: 498336) with no citations, SpliceAI 0.3 for Acceptor Loss c.1097A>G p.(Asn366Ser) (0.25 if LP but seems like VUS): not in gnomAD

v2, REVEL 0.201, not in ClinVar (CA379921132), no other cases aside from Sarkozy in LOVD, no other missense changes at same position c.1203G>A p.(Trp401Ter) (0.25 if LP): not in gnomAD v2 or v4, not in ClinVar (CA379921398), no other cases aside from Fichna in LOVD c.479G>A (p.Arg160His) (1.0 if LP): looks like VUS based on ClinVar

PP3			The computational predictor REVEL gives a score of 0.851, which exceeds the threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3).
PP4			At least one patient with this variant displayed progressive limb girdle muscle weakness (PMID: 31395899, 22402862; PP4).
PM2_Supporting			The filtering allele frequency for this variant is 0.00006 in gnomAD v4.1.0 (the upper bound of the 95% confidence interval of 57/1178734 European (non-Finnish) alleles), which is lower than the VCEP threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting). The highest MAF is in the European (Finnish) population, but we do not use that bottlenecked group.

Not Met criteria codes

PP1			Two affected family members of a proband with this variant and a second presumed diagnostic ANO5 allele were shown to have the same two variants but phase was not confirmed (PMID: 22980763; PP1 not met).
PM5			NM_213599.3(ANO5):c.241G>T (p.Asp81Tyr) Variation ID: 3752955 LP by Labcorp Genetics (formerly Invitae) but no literature cases

Curation History

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