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# *Variant: NM_213599.3(ANO5):c.692G>T (p.Gly231Val)*

Version: 1.0

*CA224418*

*2165 (ClinVar)*

**Gene**: ANO5 (HGNC:203859)
**Condition**: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 7d577c8a-190f-4025-9e0f-f0496b2ecdd5
**Approved on**: 2026/2/24
**Published on**: 2026/4/9

## *HGVS expressions*

**NM_213599.3:c.692G>T**
**NM_213599.3(ANO5):c.692G>T (p.Gly231Val)**
NC_000011.10:g.22236206G>T
CM000673.2:g.22236206G>T
NC_000011.9:g.22257752G>T
CM000673.1:g.22257752G>T
NC_000011.8:g.22214328G>T
NG_015844.1:g.48031G>T
ENST00000682266.1:c.242G>T
ENST00000682341.1:c.650G>T
ENST00000682530.1:c.*624G>T
ENST00000682684.1:n.1071G>T
ENST00000683197.1:c.650G>T
ENST00000683411.1:c.242G>T
ENST00000683437.1:c.242G>T
ENST00000683613.1:n.1686G>T
ENST00000683834.1:n.892G>T
ENST00000684663.1:c.647G>T
ENST00000324559.9:c.692G>T
ENST00000648804.1:n.1213+8620G>T
ENST00000324559.8:c.692G>T
NM_001142649.1:c.689G>T
NM_213599.2:c.692G>T
NM_001142649.2:c.689G>T

**Likely Pathogenic**

**Met criteria codes** 2

PP4 PM3_Very Strong

**Not Met criteria codes** 5

PP3 PM5 PM2 BS1 BP4

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.692G>T variant in ANO5 is a missense variant expected to result in the substitution of glycine for valine at amino acid 231, p.(Gly231Val). The Grpmax FAF for this variant is 0.002635 in gnomAD v4.1.0, which is greater than the VCEP threshold of 0.001 for BS1. However, this variant is recognized as one of the most common pathogenic variants in ANO5, and the VCEP opted not to apply this code (BS1 exception). The Total population also includes four homozygous individuals, but variants in ANO5 can be associated with mild and late onset disease, and the VCEP does not consider this evidence contradictory with the pathogenicity of this variant. Across a selection of the available data, this variant has been identified in over 20 individuals with features consistent with LGMD (PMID: 34008892, 36575883, 25891276, 32925086, 35628876, 31353849; LOVD ANO5_000005; GRASP-LGMD Consortium internal data communication). These observations include eight unrelated patients in whom it was reported in unconfirmed phase with a pathogenic variant (c.191dup p.(Asn64LysfsTer15) x6, 3.0 pts, PMID: 35628876, 31353849, GRASP-LGMD Consortium internal data communication; c.1898+1G>A, 0.5 pts, GRASP-LGMD Consortium internal data communication; c.2272C>T p.(Arg758Cys), 0.5 pts, GRASP-LGMD Consortium internal data communication) (PM3_Very Strong). This variant has also been reported in a homozygous state in at least four unrelated patients experiencing muscle weakness and with signs of atrophy or dystrophy on muscle biopsy (PMID: 25891276, 31353849). At least one patient with this variant and a second presumed diagnostic ANO5 allele exhibited limb girdle muscle weakness and had a clinical diagnosis of LGMD (PP4). The computational predictor REVEL gives a score of 0.49 (PP3, BP4 not met). In summary, this variant is classified as Likely Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications version 2.0.0, 02/24/2026): PM3_Very Strong, PP4.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP4** | ✔ | At least one patient with this variant and a second presumed diagnostic ANO5 allele exhibited limb girdle muscle weakness and had a clinical diagnosis of LGMD (PP4). |
| **PM3_Very Strong** | ✔ | Across a selection of the available data, this variant has been identified in over 20 individuals with features consistent with LGMD (PMID: 34008892, 36575883, 25891276, 32925086, 35628876, 31353849; LOVD ANO5_000005; GRASP-LGMD Consortium internal data communication). These observations include eight unrelated patients in whom it was reported in unconfirmed phase with a pathogenic variant (c.191dup p.(Asn64LysfsTer15) x6, 3.0 pts, PMID: 35628876, 31353849, GRASP-LGMD Consortium internal data communication; c.1898+1G>A, 0.5 pts, GRASP-LGMD Consortium internal data communication; c.2272C>T p.(Arg758Cys), 0.5 pts, GRASP-LGMD Consortium internal data communication). This variant has also been reported in a homozygous state in at least four unrelated patients experiencing muscle weakness and with signs of atrophy or dystrophy on muscle biopsy (PMID: 25891276, 31353849). (PM3_Very Strong) scored: c.191dup x6: 3 pt, predicted on different haplotypes c.1898+1G>A: 0.5 pt, predicted on different haplotypes c.2272C>T p.(Arg758Cys): 0.5 pt, predicted on different haplotypes symptomatic hom x4 unscored: c.2478G>T p.(Trp826Cys) (VUS) c.1359G>C p.(Tyr453Ter) x2 c.2498T>A p.(Met833Lys) c.2342T>C p.(Leu781Pro) c.40G>A p.(Gly14Arg) c.709A>G p.(Ile237Val), confirmed in trans LOVD ANO5_000005: 49 reported entries |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✖ | The computational predictor REVEL gives a score of 0.49 (PP3, BP4 not met). SpliceAI 0.15 |
| **PM5** | ✖ | no other missense variants seem to have been reported at this position |

| | | | |
|---|---|---|---|
| **PM2** | | ✖ | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| **BS1** | ℹ | ✖ | The Grpmax FAF (the lower bound of the 95% confidence interval of the maximum credible genetic ancestry group allele frequency) is 0.002635, which is greater than the VCEP threshold of 0.001 for BS1. However, this variant is recognized as one of the most common pathogenic variants in ANO5, and the VCEP opted not to apply this code (BS1 exception). 4 homozygotes in Total population: 1 65-70, 1 40-45 |
| **BP4** | ℹ | ✖ | The computational predictor REVEL gives a score of 0.49 (PP3, BP4 not met). SpliceAI 0.15 |

## Curation History

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