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Variant: NM_213599.3(ANO5):c.1295C>G (p.Ala432Gly)

Version: 1.0

CA224408

2163 (ClinVar)

Gene: ANO5 (HGNC:203859)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5f8f545e-ffe9-4fce-bb11-c491e1dcf329
Approved on: 2026/1/8
Published on: 2026/2/17

HGVS expressions

NM_213599.3(ANO5):c.1295C>G (p.Ala432Gly)
NM_213599.3:c.1295C>G
NC_000011.10:g.22255485C>G
CM000673.2:g.22255485C>G
NC_000011.9:g.22277031C>G
CM000673.1:g.22277031C>G
NC_000011.8:g.22233607C>G
NG_015844.1:g.67310C>G
ENST00000682089.1:n.615C>G
ENST00000682266.1:c.845C>G
ENST00000682341.1:c.1253C>G
ENST00000682530.1:c.*1227C>G
ENST00000683197.1:c.1253C>G
ENST00000683411.1:c.845C>G
ENST00000683437.1:c.845C>G
ENST00000683613.1:n.2289C>G
ENST00000683834.1:n.1495C>G
ENST00000684663.1:c.1250C>G
ENST00000324559.9:c.1295C>G
ENST00000648804.1:n.1630C>G
ENST00000324559.8:c.1295C>G
NM_001142649.1:c.1292C>G
NM_213599.2:c.1295C>G
NM_001142649.2:c.1292C>G

Pathogenic

Met criteria codes 5

PVS1 PP1_Strong PP4 PM3_Strong PM2_Supporting

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.1295C>G variant in ANO5 is a missense variant predicted to cause the substitution of alanine by glycine at amino acid position 432, p.(Ala432Gly). The computational predictor REVEL gives a score of 0.176, however, SpliceAI gives a delta score of 0.62 for loss of the canonical donor and 1.00 for gain of a cryptic donor 38 nucleotides into exon 13. RNA analysis has demonstrated a complete splice effect of this variant, resulting in the deletion of the last 38 nucleotides of exon 13, which is expected to lead to a frameshift, premature truncation, p.(Ala432GlyfsTer49), and subsequent nonsense mediated decay (PMID: 20096397, PVS1_RNA). This variant has been reported in at least five unrelated individuals with features consistent with LGMD (PMID: 26809617, 31353849, 20096397), including in a homozygous state in the probands of two consanguineous families sharing a common haplotype (0.25 pts x2; PMID: 20096397) and in unknown phase with a pathogenic variant in three affected individuals (c.989dupT p.(Leu330Phefs), 0.5 pts, PMID: 26809617; c.191dupA p.(Asn64LysfsTer15), 0.5 pts, PMID: 31353849; and c.2272C>T p.(Arg758Cys), 0.5 pts, PMID: 31353849) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic ANO5 allele displayed a progressive limb girdle pattern of muscle weakness (PMID: 26809617, 31353849, 20096397; PP4). This variant has also been reported to co-segregate with autosomal recessive LGMD in four affected family members from the two families sharing the same haplotype (PMID: 20096397; PP1_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000021617 (17/1179582 European (non-Finnish) chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting). 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; 01/08/2026): PVS1_RNA, PM3_Strong, PP4, PP1_Strong, PM2_Supporting.

Met criteria codes

PVS1	✔	RNA analysis has demonstrated a complete splice effect of this variant, resulting in the deletion of the last 38 nucleotides of exon 13, which is expected to lead to a frameshift, premature truncation, p.(Ala432GlyfsTer49), and subsequent nonsense mediated decay (PMID: 20096397, PVS1_RNA).
PP1_Strong	✔	This variant has also been reported to co-segregate with autosomal recessive LGMD in four affected family members from two families sharing the same haplotype (PMID: 20096397; PP1_Strong). Both families had an individual over 60 years who was homozygous for the variant and reporting no symptoms. However, raised CK and mild iliopsoas weakness (MRC <5) was identified in both individuals on exam, and they were described as 'affected' multiple times in paper. For these reasons, we opted to include these individuals as segregations.
PP4	✔	At least one patient with this variant and a second presumed diagnostic ANO5 allele displayed a progressive limb girdle pattern of muscle weakness (PMID: 26809617, 31353849, 20096397; PP4).
PM3_Strong	✔	This variant has been reported in at least five unrelated individuals with features consistent with LGMD (PMID: 26809617, 31353849, 20096397), including in a homozygous state in the probands of two consanguineous families sharing a common haplotype (0.25 pts x2; PMID: 20096397) and in unknown phase with a pathogenic variant in three affected individuals (c.989dupT p.(Leu330Phefs), 0.5 pts, PMID: 26809617; c.191dupA p.(Asn64LysfsTer15), 0.5 pts, PMID: 31353849; and c.2272C>T p.(Arg758Cys), 0.5 pts, PMID: 31353849) (PM3_Strong).
PM2_Supporting	✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000021617 (17/1179582 European (non-Finnish) chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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