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Variant: NM_213599.3(ANO5):c.989dup (p.Leu330fs)

Version: 1.0

CA200776

96688 (ClinVar)

Gene: ANO5 (HGNC:203859)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 38ac391a-ef60-4c55-bf4d-528fc3e8ece4
Approved on: 2025/1/7
Published on: 2025/1/7

HGVS expressions

NM_213599.3:c.989dup
NM_213599.3(ANO5):c.989dup (p.Leu330fs)
NC_000011.10:g.22250347dup
CM000673.2:g.22250347dup
NC_000011.9:g.22271893dup
CM000673.1:g.22271893dup
NC_000011.8:g.22228469dup
NG_015844.1:g.62172dup
ENST00000682089.1:n.309dup
ENST00000682266.1:c.539dup
ENST00000682341.1:c.947dup
ENST00000682530.1:c.*921dup
ENST00000683197.1:c.947dup
ENST00000683411.1:c.539dup
ENST00000683437.1:c.539dup
ENST00000683613.1:n.1983dup
ENST00000683834.1:n.1189dup
ENST00000684663.1:c.944dup
ENST00000324559.9:c.989dup
ENST00000648804.1:n.1324dup
ENST00000324559.8:c.989dup
NM_001142649.1:c.986dup
NM_213599.2:c.989dup
NM_001142649.2:c.986dup

Pathogenic

Met criteria codes 3

PVS1 PM3 PP4

Not Met criteria codes 2

PM2 PM4

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 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.989dup (p.Leu330PhefsTer6)) variant in ANO5 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 10/22, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least one individual with progressive limb girdle muscle weakness, where it was confirmed in trans with a likely pathogenic or pathogenic variant (c.304_308del p.(Lys102fs), 1.0 pt, PMID: 27862037) (PM3, PP4). The filtering allele frequency of this variant is 0.000116 (the upper threshold of the 95% CI of 7/113346 European (non-Finnish) exome chromosomes) in gnomAD v2.1.1, which is above the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). 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 1.0.0; 01/07/2025): PVS1, PM3, PP4.

Met criteria codes

PVS1	✔	The c.989dup (p.Leu330fs) variant in ANO5 is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 10/22 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3	✔	This variant has been detected in at least 1 individual with LGMD2L, who was compound heterozygous for the variant and a pathogenic or likely pathogenic variant. This individual was confirmed in trans by family testing (c.304_308del (p.Lys102fs)); potential PM3 points = 1, PMID: 27862037).
PP4	✔	At least one patient with this variant displayed progressive weakness, dystrophic features on biopsy, and elevated CK levels, which is highly specific for LGMD2L (PP4_Supporting, PMID: 27862037).

Not Met criteria codes

PM2	✖	The filtering allele frequency (the upper threshold of the 95% CI of 9/250760) of the c.989dup variant in ANO5 is 0.00006263 for European (non-Finnish) chromosomes by gnomAD v2.1.1, which is lower than the ClinGen LGMD threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). EDIT: PM2_Supporting removed as ConfIT de MAF gives upper 95% CI of 0.0001121
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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