

Variant: *NM_213599.3(ANO5):c.2272C>T (p.Arg758Cys)*

Version: 1.0

CA130516 [↗](#)

2166 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fbaa9261-0755-4e95-80b7-9e2d4a82b2ed

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HGVS expressions

NM_213599.3:c.2272C>T

NM_213599.3(ANO5):c.2272C>T (p.Arg758Cys)

NC_000011.10:g.22274605C>T

CM000673.2:g.22274605C>T

NC_000011.9:g.22296151C>T

CM000673.1:g.22296151C>T

NC_000011.8:g.22252727C>T

NG_015844.1:g.86430C>T

ENST00000532043.2:n.289C>T

ENST00000682266.1:c.1822C>T

ENST00000682341.1:c.2230C>T

ENST00000683197.1:c.2230C>T

ENST00000683411.1:c.1822C>T

ENST00000683437.1:c.1822C>T

ENST00000683613.1:n.3266C>T

ENST00000684663.1:c.2227C>T

ENST00000324559.9:c.2272C>T

ENST00000648804.1:n.2607C>T

ENST00000324559.8:c.2272C>T

ENST00000532043.1:n.289C>T

NM_001142649.1:c.2269C>T

NM_213599.2:c.2272C>T

NM_001142649.2:c.2269C>T

Pathogenic

Met criteria codes 4

PP1_Strong

PM3_Very Strong

PP3

PP4

Not Met criteria codes 22

PVS1

BA1

BP5

BP7

BP4

BP3

BP1

BP2

BS2

BS1

BS4

BS3

PP2

PM6

PM2

PM1

PM5

PM4

PS1

PS2

PS3

PS4

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.2272C>T variant in ANO5 is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 758 (p.Arg758Cys). This variant has been detected in at least 7 individuals with LGMD, five of whom had a second ANO5 variant classified as pathogenic or likely pathogenic, with one confirmed in trans by parental testing (c.191dup x5, 3.0 pts, PMID: 25135358, 24803842, 21739273, 21186264). Two patients were homozygous for the variant (1.0 pt, PMID: 20096397) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness (PP4; PMID: 31395899). The variant has been reported to segregate with LGMD in six affected family members from three families (PP1_Strong; PMID: 20096397, 27911336). The maximum minor allele frequency for this variant is 0.0003116 (40/128354 chromosomes) in the European (non-Finnish) population in gnomAD v2.1.1, which exceeds the VCEP threshold of 0.0001 for PM2 (criterion not met). The computational predictor REVEL gives a score of 0.82, which meets the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3). 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): PM3_Very Strong, PP4, PP1_Strong, PP3.

Met criteria codes

PP1_Strong			The variant has been reported to segregate with LGMD 2L in 6 affected family members from 3 families (PP1_Strong; PMID: 20096397, 27911336).
PM3_Very Strong			This variant has been detected in at least 7 individuals with LGMD 2L. Of those individuals, 5 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 1 of those were confirmed in trans by parental testing (c.191dup x5, 3.0pt, PMIDs: 25135358, 24803842, 21739273, 21186264). 2 individuals were homozygous for the variant (1.0pt, PMID: 20096397) (PM3_VeryStrong).
PP3			The computational predictor REVEL gives a score of 0.82, which meets the threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3).
PP4			At least one patient with this variant displayed progressive weakness, which is specific for LGMD 2L (PP4_supporting, PMID: 31395899).

Not Met criteria codes

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			European (non-Finnish) calculated = 0.00631 --> 0.0063 [[CODE CAN'T BE MET]]
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			c.2273G>A [p.Arg758His] = UNCERTAIN SIGNIFICANCE
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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