

Variant: *NM_213599.3(ANO5):c.2018A>G (p.Tyr673Cys)*

Version: 1.0

CA232789 [↗](#)

140555 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1011713c-b155-4165-9bec-be5fdb84e664

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HGVS expressions

NM_213599.3(ANO5):c.2018A>G (p.Tyr673Cys)

NM_213599.3:c.2018A>G

NC_000011.10:g.22270431A>G

CM000673.2:g.22270431A>G

NC_000011.9:g.22291977A>G

CM000673.1:g.22291977A>G

NC_000011.8:g.22248553A>G

NG_015844.1:g.82256A>G

ENST00000532043.2:n.35A>G

ENST00000682266.1:c.1568A>G

ENST00000682341.1:c.1976A>G

ENST00000683197.1:c.1976A>G

ENST00000683411.1:c.1568A>G

ENST00000683437.1:c.1568A>G

ENST00000683613.1:n.3012A>G

ENST00000684663.1:c.1973A>G

ENST00000324559.9:c.2018A>G

ENST00000648804.1:n.2353A>G

ENST00000324559.8:c.2018A>G

ENST00000532043.1:n.35A>G

NM_001142649.1:c.2015A>G

NM_213599.2:c.2018A>G

NM_001142649.2:c.2015A>G

Pathogenic

Met criteria codes 5

PM3_Strong

PP3

PP4

PP1_Strong

PM2_Supporting

Not Met criteria codes 21

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP2

PM6

PS1

PS2

PS3

PS4

BA1

PM1

PM5

PM4

PVS1

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**

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.2018A>G variant in ANO5 is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 673 (p.Tyr673Cys). This variant has been detected in at least 6 individuals with autosomal recessive limb-girdle muscular dystrophy. Of those individuals, five had another pathogenic or likely pathogenic variant, with three confirmed in trans by parental testing (c.191dup x2, 2 pts, PMIDs: 21820307, 21186264) and two phase unknown (c.191dup, 0.5 pts, ClinVar SCV001371267.12 internal data communication; c.989dup, 0.5 pts, PMID: 23606453). One individual was homozygous for the variant (0.5 pts, ClinVar SCV000767092.3 internal data communication) (PM3_Strong). At least one patient with this variant displayed a progressive limb girdle pattern of muscle weakness (PP4; PMD: 21820307). The variant has been reported to segregate with the LGMD phenotype in four affected family members from two families (PP1_Strong; PMID: 21186264, 23670307). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (1/15424 alleles) in the European (non-Finnish) population, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.88, which exceeds 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_Strong, PP1_Strong, PP4, PM2_Supporting, PP3.

Met criteria codes

PM3_Strong			This variant has been detected in at least 6 individuals with autosomal recessive limb-girdle muscular dystrophy. Of those individuals, 5 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant, with 3 of those confirmed in trans by parental testing (c.191dup x2, 2 pt, PMIDs: 21820307, 21186264) and 2 were phase unknown (c.191dup, 0.5 pt, ClinVar SCV001371267.12; c.989dup, 0.5 pts, PMID: 23606453). 1 individual was homozygous for the variant (0.5pt, ClinVar SCV000767092.3). A total of 3.5 pts meet criteria for PM3_Strong.
PP3			The computational predictor REVEL gives a score of 0.884, 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 weakness, which is specific for autosomal recessive limb-girdle muscular dystrophy (PP4_Supporting, PMD: 21820307).
PP1_Strong			The variant has been reported to segregate with autosomal recessive limb-girdle muscular dystrophy in 2 affected family members from 2 families (PP1_Strong; PMID: 21186264, 23670307).
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (1/15424 alleles) in European (non-Finnish) population, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

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
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
BS2		✖	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
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

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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