

Variant: *NR_135553.2:n.649C>T*

Version: 1.0

CA400180431 [↗](#)

Gene: SGCA ([HGNC:6442](#))

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 48c0b2b6-40e6-4b99-a6a5-d6bdc5b64264

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HGVS expressions

NR_135553.2:n.649C>T

NC_000017.11:g.50169120C>T

CM000679.2:g.50169120C>T

NC_000017.10:g.48246481C>T

CM000679.1:g.48246481C>T

NC_000017.9:g.45601480C>T

NG_008889.1:g.8116C>T

ENST00000504073.2:c.597+16C>T

ENST00000511303.6:n.309+548C>T

ENST00000512526.2:c.575+548C>T

ENST00000682109.1:c.493C>T

ENST00000683226.1:n.323C>T

ENST00000683294.1:c.613C>T

ENST00000262018.8:c.613C>T

ENST00000262018.7:c.613C>T

ENST00000344627.10:c.584+548C>T

ENST00000502555.5:c.*272C>T

ENST00000504073.1:c.64+16C>T

ENST00000511303.5:c.305+548C>T

ENST00000512526.1:c.419+548C>T

ENST00000513821.5:c.613C>T

ENST00000513942.5:n.375+548C>T

NM_000023.2:c.613C>T

NM_001135697.1:c.584+548C>T

NM_000023.3:c.613C>T

NM_001135697.2:c.584+548C>T

NR_135553.1:n.669C>T

NM_000023.4:c.613C>T

NM_001135697.3:c.584+548C>T

Pathogenic

Met criteria codes **6**

PM3_Supporting

PS3_Moderate

PP3

PM5_Supporting

PP4_Strong

PM2_Supporting

Expert Panel

Limb Girdle Muscular Dystrophy VCEP [↗](#)

Criteria Specification Information

Not Met criteria codes 1

PP1

Evidence Links 0

[Criteria Specification: ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SGCA 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_000023.4: c.613C>T variant in SGCA is a missense variant predicted to cause substitution of proline by serine at amino acid 205, p.(Pro205Ser). This variant has been detected in at least two individuals with limb girdle muscular dystrophy (Newcastle University, GRASP-LGMD Consortium internal data communication), including in unconfirmed phase with a pathogenic variant in one case (c.229C>T p.(Arg77Cys), 0.5 pt, Newcastle University internal data communication) (PM3_Supporting). At least one patient with this variant and a second presumed diagnostic SGCA variant displayed both progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression in skeletal muscle, which is highly specific for SGCA-related LGMD (PP4_Strong; Newcastle University, GRASP-LGMD Consortium internal data communication). The variant has been reported to segregate with limb-girdle muscular dystrophy in two affected siblings from one family, but phase was not confirmed (Newcastle University internal data communication). The Grpmax variant allele frequency is 0.000011 in gnomAD v4.1.1 (1/91088 South Asian alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion. An in vitro assay in a heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex (PS3_Moderate; Washington University internal data communication). In addition, the computational predictor REVEL gives a score of 0.815, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3). Another missense variant affecting the same codon, c.614C>A p.(Pro205His), has also been classified as likely pathogenic for autosomal recessive limb-girdle muscular dystrophy by the ClinGen LGMD VCEP (PM5_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 (specification guidelines v2.0.0; 04/29/2026): PM3_Supporting, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3, PM5_Supporting.

Met criteria codes

PM3_Supporting			This variant has been detected in at least two individuals with limb girdle muscular dystrophy (Newcastle University, GRASP-LGMD Consortium internal data communication), including in unconfirmed phase with a pathogenic variant in one case (c.229C>T p.(Arg77Cys), 0.5 pt, Newcastle University internal data communication) (PM3_Supporting). GnomAD Variant co-Occurrence cannot be implemented as variant c.265C>T is not present in GnomAD v.2. The second (GRASP) patient has c.265C>T p.(Leu89Phe), which is a VUS without the PP4_Strong evidence from this case.
PS3_Moderate			In vitro assay in an heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex (PS3_Moderate, Washington University internal data). Variant was tested by Gabe Haller's team using their previously reported approach for SGCB variants. The assay has been clinically validated with over 11 control variants. The variant presented a score <-0.5 (-0.71), which is the threshold for non-functional variants that was used for SGCB. Score -1.88 in complementary assay done in the Lek lab at Yale. (concordant)
PP3			The computational predictor REVEL gives a score of 0.815, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3). SpliceAI: 0.100
PM5_Supporting			Another missense variant affecting the same codon, c.614C>A p.(Pro205His), has been classified as likely pathogenic for autosomal recessive limb-girdle muscular dystrophy by the ClinGen LGMD VCEP (PM5_Supporting). NM_000023.4(SGCA):c.614C>A p.(Pro205His) SpliceAI: 0.0800 LP without use of PM5 The REVEL score for the curated variant is >0.7, and the SpliceAI scores for both curated and comparison variant are <0.5

PP4_Strong			At least one patient with this variant and a second presumed diagnostic SGCA variant displayed both progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression in skeletal muscle, which is highly specific for SGCA-related LGMD (PP4_Strong; Newcastle University, GRASP-LGMD Consortium internal data communication).
PM2_Supporting			The Grpmax variant allele frequency is 0.000011 in gnomAD v4.1.1 (1/91088 South Asian alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion.
Not Met criteria codes			
PP1			The variant has been reported to segregate with limb-girdle muscular dystrophy in two affected siblings from one family, but phase was not confirmed (Newcastle University internal data communication).

Curation History 			
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