

Variant: *NM_000023.4(SGCA):c.265C>T (p.Leu89Phe)*

Version: 1.0

CA400177739 [↗](#)

659203 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 96fc569e-0633-4821-9740-c8abec3eca27

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HGVS expressions

NM_000023.4:c.265C>T

NM_000023.4(SGCA):c.265C>T (p.Leu89Phe)

NC_000017.11:g.50167689C>T

CM000679.2:g.50167689C>T

NC_000017.10:g.48245050C>T

CM000679.1:g.48245050C>T

NC_000017.9:g.45600049C>T

NG_008889.1:g.6685C>T

ENST00000504073.2:c.265C>T

ENST00000511303.6:n.38-258C>T

ENST00000512526.2:c.265C>T

ENST00000682109.1:c.145C>T

ENST00000683294.1:c.265C>T

ENST00000262018.8:c.265C>T

ENST00000262018.7:c.265C>T

ENST00000344627.10:c.265C>T

ENST00000502555.5:c.157+202C>T

ENST00000511303.5:c.34-258C>T

ENST00000512526.1:c.109C>T

ENST00000513821.5:c.265C>T

ENST00000513942.5:n.104-258C>T

ENST00000514934.1:c.*18+202C>T

NM_000023.2:c.265C>T

NM_001135697.1:c.265C>T

NM_000023.3:c.265C>T

NM_001135697.2:c.265C>T

NR_135553.1:n.321C>T

NM_001135697.3:c.265C>T

NR_135553.2:n.301C>T

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PP3

PP4_Strong

PS3_Moderate

Not Met criteria codes **1**

Expert Panel

Limb Girdle Muscular Dystrophy VCEP [↗](#)

Criteria Specification Information

PM3

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.265C>T variant in SGCA is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 89, p.(Leu89Phe). This variant has been detected in at least one individual with limb girdle muscular dystrophy, where it was reported in unconfirmed phase with a likely pathogenic variant (c.613C>T p.(Pro205Ser), 0.25 pts, GRASP-LGMD Consortium, Newcastle University internal data communication) (PM3_Supporting not met). This patient displayed progressive limb girdle muscle weakness and significantly reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000014 (10/1179660 European (non-Finnish) 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). The computational predictor REVEL also gives a score of 0.836, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive limb-girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specification guidelines for SGCA version v2.0.0; 04/29/2026): PP4_Strong, PS3_Moderate, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting			The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000014 (10/1179660 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion.
PP3			The computational predictor REVEL gives a score of 0.836, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3).
PP4_Strong			This patient displayed progressive limb girdle muscle weakness and significantly reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Strong; GRASP-LGMD Consortium, Newcastle University internal data communication).
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 (-1.079), which is the threshold for non-functional variants that was used for SGCB. Score -2.04 in complementary assay done in the Lek lab at Yale.

Not Met criteria codes

PM3			This variant has been detected in at least one individual with limb girdle muscular dystrophy, where it was reported in unconfirmed phase with a likely pathogenic variant (c.613C>T p.(Pro205Ser), 0.25 pts, GRASP-LGMD Consortium, Newcastle University internal data communication) (PM3 not met).
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Curation History 		
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