

Variant: NM_000023.4(SGCA):c.614C>A (p.Pro205His)

Version: 1.0

CA501043 [↗](#)

289794 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 929ac2ff-cd52-4f98-a008-6c798511c27e

Approved on: 2026/5/1

Published on: 2026/5/7

HGVS expressions

NM_000023.4:c.614C>A

NM_000023.4(SGCA):c.614C>A (p.Pro205His)

NC_000017.11:g.50169121C>A

CM000679.2:g.50169121C>A

NC_000017.10:g.48246482C>A

CM000679.1:g.48246482C>A

NC_000017.9:g.45601481C>A

NG_008889.1:g.8117C>A

ENST00000504073.2:c.597+17C>A

ENST00000511303.6:n.309+549C>A

ENST00000512526.2:c.575+549C>A

ENST00000682109.1:c.494C>A

ENST00000683226.1:n.324C>A

ENST00000683294.1:c.614C>A

ENST00000262018.8:c.614C>A

ENST00000262018.7:c.614C>A

ENST00000344627.10:c.584+549C>A

ENST00000502555.5:c.*273C>A

ENST00000504073.1:c.64+17C>A

ENST00000511303.5:c.305+549C>A

ENST00000512526.1:c.419+549C>A

ENST00000513821.5:c.614C>A

ENST00000513942.5:n.375+549C>A

NM_000023.2:c.614C>A

NM_001135697.1:c.584+549C>A

NM_000023.3:c.614C>A

NM_001135697.2:c.584+549C>A

NR_135553.1:n.670C>A

NM_001135697.3:c.584+549C>A

NR_135553.2:n.650C>A

Likely Pathogenic

Met criteria codes 4

PP3PP4PM3_StrongPS3_Moderate

Not Met criteria codes 3

BS1PM2PM5

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 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.614C>A variant in SGCA is a missense variant predicted to cause substitution of proline by histidine at amino acid 205, p.(Pro205His). This variant has been detected in at least five individuals with limb-girdle muscular dystrophy, including in a homozygous state in two patients, one with reported consanguinity (0.75 pts; PMID: 35948506; LOVD Individual #00468440). Three patients were presumed compound heterozygous for the variant and a second pathogenic variant (c.409G>A p.(Glu137Lys), 0.5 pts x2, PMID: 31069529, 9032047; c.269A>G p.(Tyr90Cys), 0.5 pts, GRASP-LGMD Consortium internal data communication). (PM3_Strong) At least one patient heterozygous for this variant and a second diagnostic SGCA variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD, but SGCD was not included in the genetic analysis (PP4; PMID: 9032047). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0001404 (5/74894 African/African-American alleles), which is higher than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore does not meet this criterion. An 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 communication). The computational predictor REVEL gives a score of 0.84, 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 (LGMD VCEP specifications version 2.0.0; 05/01/2026): PM3_Strong, PP4, PS3_Moderate, PP3.

Met criteria codes

PP3

The computational predictor REVEL gives a score of 0.84, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3). SpliceAI: 0.0800

PP4

At least one patient heterozygous for this variant and a second diagnostic SGCA variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD, but SGCD was not included in the genetic analysis (PP4; PMID: 9032047).

PM3_Strong

This variant has been detected in at least five individuals with limb-girdle muscular dystrophy, including in a homozygous state in two patients, one with reported consanguinity (0.75 pts; PMID: 35948506; LOVD Individual #00468440). Three patients were presumed compound heterozygous for the variant and a second pathogenic variant (c.409G>A p.(Glu137Lys), 0.5 pts x2, PMID: 31069529, 9032047; c.269A>G p.(Tyr90Cys), 0.5 pts, GRASP-LGMD Consortium internal data communication). (PM3_Strong) co-occurrence checked

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, which is the threshold for non-functional variants that was used for SG. Score -0.91 in WashU assay, -0.7 in Lek/Yale assay

Not Met criteria codes

BS1			The filtering allele frequency of the variant is 0.000026306 for African/African-American alleles in gnomAD v4.1.0 (the lower threshold of the 95% CI of 5/74894), which is lower than the LGMD VCEP threshold (>0.0009) for BS1, and therefore does not meet this criterion.
PM2			The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0001404 (5/74894 African/African-American alleles), which is higher than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore does not meet this criterion.
PM5			NM_000023.4(SGCA):c.614C>T (p.Pro205Leu) is conflicting in ClinVar

Curation History



 

 

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