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

PP3 PP4 PM3_Strong PS3_Moderate

Not Met criteria codes 3

PM2 PM5 BS1

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

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
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.

Curation History

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