

Variant: NM_000023.4(SGCA):c.320C>T (p.Ala107Val)

Version: 2.0

CA245046 [↗](#)

197094 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

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HGVS expressions

NM_000023.4(SGCA):c.320C>T (p.Ala107Val)

NM_000023.4:c.320C>T

NC_000017.11:g.50167954C>T

CM000679.2:g.50167954C>T

NC_000017.10:g.48245315C>T

CM000679.1:g.48245315C>T

NC_000017.9:g.45600314C>T

NG_008889.1:g.6950C>T

ENST00000504073.2:c.320C>T

ENST00000511303.6:n.45C>T

ENST00000512526.2:c.311C>T

ENST00000682109.1:c.200C>T

ENST00000683226.1:n.30C>T

ENST00000683294.1:c.320C>T

ENST00000262018.8:c.320C>T

ENST00000262018.7:c.320C>T

ENST00000344627.10:c.320C>T

ENST00000502555.5:c.165C>T

ENST00000511303.5:c.41C>T

ENST00000512526.1:c.155C>T

ENST00000513821.5:c.320C>T

ENST00000513942.5:n.111C>T

ENST00000514934.1:c.*26C>T

NM_000023.2:c.320C>T

NM_001135697.1:c.320C>T

NM_000023.3:c.320C>T

NM_001135697.2:c.320C>T

NR_135553.1:n.376C>T

NM_001135697.3:c.320C>T

NR_135553.2:n.356C>T

Likely Pathogenic

Met criteria codes 2

PM3_Very StrongPP3

Not Met criteria codes 5

BS1PS3BA1PP4PM2

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.320C>T variant in SGCA is a missense variant predicted to cause substitution of alanine by valine at amino acid 170, p.(Ala107Val). This variant has been reported confirmed in trans with another SGCA variant in 8 unrelated East Asian patients with reduced sarcoglycan protein expression in skeletal muscle and clinical features consistent with LGMD or sarcoglycanopathy, although it was typically associated with a mild presentation, with some patients presenting with hyperCKemia only (PMID: 39755676, 30764848, 28403181). Five patients had a likely pathogenic or pathogenic variant confirmed in trans (c.229C>T p.(Arg77Cys), 1.0 pt x3, PMID: 39755676; c.662G>C p.(Arg221Pro), 1.0 pt, PMID: 39755676; c.661C>T p.(Arg221Cys), 1.0 pt, PMID: 30764848, 28403181) (PM3_Very Strong). All of the reported compound heterozygous Japanese patients had significantly reduced expression of sarcoglycan in skeletal muscle by immunohistochemistry, and some were also reported to have limb girdle muscle weakness. However, progression in individual patients was not clearly described (PMID: 39755676; PP4 not met). The Grpmax FAF (the lower bound of the 95% confidence interval of the maximum credible genetic ancestry group allele frequency) is 0.0023 in gnomAD v4.1.1 (123/44882 East Asian chromosomes), which is higher than the ClinGen Limb Girdle Muscular Dystrophy Expert Panel threshold (0.002) for BA1. However, this variant is one of the most common SGCA variants identified in Japanese patients, where it has been associated with a mild phenotype (PMID: 39755676), and the VCEP opted not to apply this code (BA1 exception). The computational predictor REVEL gives a score of 0.864, which is above the threshold of 0.70, 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; 04/28/2026): PM3_Very Strong, PP3.

Met criteria codes

PM3_Very Strong	 	This variant has been reported confirmed in trans with another SGCA variant in 8 unrelated East Asian patients with reduced sarcoglycan protein expression in skeletal muscle and clinical features consistent with LGMD or sarcoglycanopathy, although it was typically associated with a mild presentation (PMID: 39755676, 30764848, 28403181). Five patients had a likely pathogenic or pathogenic variant confirmed in trans (c.229C>T p.(Arg77Cys), 1.0 pt x3, PMID: 39755676; c.662G>C p.(Arg221Pro), 1.0 pt, PMID: 39755676; c.661C>T p.(Arg221Cys), 1.0 pt, PMID: 30764848, 28403181) (PM3_Very Strong). c.38-2A>C c.229C>T p.(Arg77Cys) x3: VCEP P c.271G>A p.(Gly91Ser): LP/P in ClinVar c.409_410delinsCCTGGTGCGCAGCCAGG, p.(E137delinsPGAQPG) c.662G>C p.(Arg221Pro): VCEP LP c.661C>T p.(Arg221Cys): VCEP LP c.38-2A>C, p.(E137delinsPGAQPG), c.662G>C p.(Arg221Pro): absent gnomAD v2 c.229C>T p.(Arg77Cys), c.271G>A p.(Gly91Ser), c.661C>T (p.Arg221Cys): predicted on different haplotypes in gnomAD v2
PP3	 	The computational predictor REVEL gives a score of 0.864, which is above the threshold of 0.70, evidence that correlates with impact to SGCA function (PP3).

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			Indeterminate result in an in vitro assay of membrane localization of the sarcoglycan complex (Washington University internal data). functional score in WashU assay: -0.33 (cut-off for PS3_Moderate: -0.5) largely concordant result in Lek/Yale assay: -1.5 (no cut-off determined)
BA1			The Grpmax FAF (the lower bound of the 95% confidence interval of the maximum credible genetic ancestry group allele frequency) is 0.0023 in gnomAD v4.1.1 (123/44882 East Asian chromosomes), which is higher than the ClinGen Limb Girdle Muscular Dystrophy Expert Panel threshold (0.002) for BA1. However, this variant appear to be one of the most commonly described SGCA variants reported in Japanese patients, where it has been associated with a mild phenotype (PMID: 39755676), and the VCEP opted not to apply this code (BA1 exception). No homozygotes in Total from Vijay about co-occurrence in gnomAD v2: "it's seen in trans with only 1 other ClinVar variant (a B/LB variant). It's not seen in trans with any ClinVar P/LP variants. We don't yet have a statistic to tell you how "unlikely" this is (i.e., an equivalent of an "observed/expected" metric), but we're working on it. So take it with a grain of salt for now, but yes I think it's reasonable that this could be a hypomorphic variant that's tolerated as a homozygote but not as a compound het with a more damaging variant." In Shimazaki et al., 30 Japanese patients with SGCA variants: 7/60 alleles with c.320C>T (p.Ala107Val) = MAF 11.7% vs FAF 0.23% for East Asian (50x higher), but this cohort had additional requirement of 2 SGCA variants + reduced protein expression. They did not do haplotype analysis for this variant.
PP4			All of the reported compound heterozygous Japanese patients had significantly reduced expression of sarcoglycan in skeletal muscle by immunohistochemistry and some were also reported to have limb girdle muscle weakness. However, progression in these patients was not clearly described. Some patients presented with only hyperCKemia (PMID: 39755676). Retrospective study with limited individual phenotype details. Patients seem to have been identified based on genetic test and protein expression findings rather than clinically.
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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