

Variant: NM_000023.4(SGCA):c.292C>T (p.Arg98Cys)

Version: 1.0

CA8643744 [↗](#)

284708 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 15983f27-2047-43a6-95f1-a6e87c9f4bba

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HGVS expressions

NM_000023.4(SGCA):c.292C>T (p.Arg98Cys)

NM_000023.4:c.292C>T

NC_000017.11:g.50167716C>T

CM000679.2:g.50167716C>T

NC_000017.10:g.48245077C>T

CM000679.1:g.48245077C>T

NC_000017.9:g.45600076C>T

NG_008889.1:g.6712C>T

ENST00000504073.2:c.292C>T

ENST00000511303.6:n.38-231C>T

ENST00000512526.2:c.292C>T

ENST00000682109.1:c.172C>T

ENST00000683226.1:n.2C>T

ENST00000683294.1:c.292C>T

ENST00000262018.8:c.292C>T

ENST00000262018.7:c.292C>T

ENST00000344627.10:c.292C>T

ENST00000502555.5:c.157+229C>T

ENST00000511303.5:c.34-231C>T

ENST00000512526.1:c.136C>T

ENST00000513821.5:c.292C>T

ENST00000513942.5:n.104-231C>T

ENST00000514934.1:c.*18+229C>T

NM_000023.2:c.292C>T

NM_001135697.1:c.292C>T

NM_000023.3:c.292C>T

NM_001135697.2:c.292C>T

NR_135553.1:n.348C>T

NM_001135697.3:c.292C>T

NR_135553.2:n.328C>T

Pathogenic

Met criteria codes 4

PM3_Strong

PS3_Moderate

PP1

PP4_Strong

Not Met criteria codes 4

BS1

PP3

PM2

PM5

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.292C>T variant in SGCA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 98, p.(Arg98Cys). This variant has been detected in at least five individuals with limb-girdle muscular dystrophy (PMID: 17994539, 39678382, 30564623, 7668821). Of those individuals, one was confirmed compound heterozygous for the variant and a second pathogenic variant (c.293G>A p.(Arg98His), 1.0 pt, PMID: 7668821), and two were presumed compound heterozygous (phase not confirmed) for the variant and a second pathogenic variant (c.271G>A p.(Gly91Ser), 0.5 pts, PMID: 17994539; c.850C>T p.(Arg284Cys), 0.5 pts, PMID: 39678382). Another two individuals were homozygous without reported consanguinity (0.5 pts x2, PMID: 30564623, 39678382, LOVD Individual #00221203) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic SGCA variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression in skeletal muscle, which is highly specific for SGCA-related LGMD (PP4_Strong; PMID: 17994539). It has also been shown to segregate with autosomal recessive limb girdle muscular dystrophy in two affected individuals from one family (PP1; PMID: 17994539). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0007244 (42/74988 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 a heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex, indicating disruption of protein function (PS3_Moderate, Washington University internal data). The computational predictor REVEL gives a score of 0.659, which is below the threshold of 0.7 (PP3 not met). 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 (LGMD VCEP specifications version 2.0.0; 04/29/2026): PM3_Strong, PP4_Strong, PP1, PS3_Moderate.

Met criteria codes

PM3_Strong			This variant has been detected in at least five individuals with limb-girdle muscular dystrophy (PMID: 17994539, 39678382, 30564623, 7668821). Of those individuals, one was confirmed compound heterozygous for the variant and a second pathogenic variant (c.293G>A p.(Arg98His), 1.0 pt, PMID: 7668821), and two were presumed compound heterozygous (phase not confirmed) for the variant and a second pathogenic variant (c.271G>A p.(Gly91Ser), 0.5 pts, PMID: 17994539; c.850C>T p.(Arg284Cys), 0.5 pts, PMID: 39678382). Another two individuals were homozygous without reported consanguinity (0.5 pts x2, PMID: 30564623, 39678382, LOVD Individual #00221203) (PM3_Strong). co-occurence checked
PS3_Moderate			An in vitro assay in a heterologous cell system has demonstrated that this variant disrupts membrane localization of the sarcoglycan complex, indicating disruption of protein function (PS3_Moderate, Washington University internal data). score -1.42 (WashU assay), -1.6 (Lek Yale assay)
PP1			The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in two affected individuals from one family (PP1; PMID: 17994539).
PP4_Strong			At least one patient with this variant and a second presumed diagnostic SGCA variant displayed progressive limb girdle muscle weakness and absent alpha-sarcoglycan protein expression in skeletal muscle, which is highly specific for SGCA-related LGMD (PP4_Strong; PMID: 17994539).

Not Met criteria codes

BS1			The filtering allele frequency of the variant is 0.0004259 for African/African-American alleles in gnomAD v4.1.0 (the lower threshold of the 95% CI of 42/74988), which is lower than the LGMD VCEP threshold (>0.0009) for BS1, and therefore does not meet this criterion.
PP3			

The computational predictor REVEL gives a score of 0.659, which is below the threshold of 0.7 (PP3 not met). Located 7 amino acids to the end of the exon. SpliceAI: 0.00 Genie: NIF-ML Score: 0.0 Benign: 100% SpliceVault Top-10: Exon skipping of exon 3 seems to occur naturally and frequently according to GTEx and SRA. Conclusion: -Variant does not affect the assessed donor region (-4 to +8). -No cryptic Risk		
PM2		The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0007244 (42/74988 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	 	Another missense variantNM_000023.4(SGCA):c.293G>A (p.Arg98His) [ClinVar Variation ID: 9435] in the same codon has been classified as pathogenic for SGCA-related limb-girdle muscular dystrophy by the ClinGen Limb Girdle Muscular Dystrophy Expert Panel, but it cannot be applied as REVEL score of the variant under curation is <0.7.

Curation History

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