The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000232.5(SGCB):c.271C>T (p.Arg91Cys)

Version: 1.0

CA2918445

499193 (ClinVar)

Gene: SGCB (HGNC:6443)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: be0ff888-b827-49b8-9dd0-23b5e33d469a
Approved on: 2025-01-09
Published on: 2025-01-09

HGVS expressions

NM_000232.5:c.271C>T
NM_000232.5(SGCB):c.271C>T (p.Arg91Cys)
NC_000004.12:g.52029836G>A
CM000666.2:g.52029836G>A
NC_000004.11:g.52896002G>A
CM000666.1:g.52896002G>A
NC_000004.10:g.52590759G>A
NG_008891.1:g.13484C>T
ENST00000381431.10:c.271C>T
ENST00000381431.9:c.271C>T
ENST00000506357.5:c.354C>T
ENST00000514133.1:c.348C>T
NM_000232.4:c.271C>T

Pathogenic

Met criteria codes 5

PM3_Strong PP3 PP4 PP1_Moderate PS3_Moderate

Not Met criteria codes 2

PM2 BS3

Evidence Links 1

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 SGCB Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000232.5: c.271C>T variant in SGCB is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 91 p.(Arg91Cys). This variant has been detected in at least five individuals with signs of limb girdle muscular dystrophy, including in a homozygous state in families from the Plain community (0.5 pts; PMID: 35416532, 9565988) and confirmed in trans with a pathogenic variant in two cases (c.85A>T p.(Arg29Ter), 2.0 pts, PMID: 17994539, 11369190) (PM3_Strong). At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed severely reduced expression of β-sarcoglycan in skeletal muscle,

which is highly specific for SGCB-related LGMD (PMID: 11369190); however, the presence of potentially diagnostic variants in all of the other three sarcoglycan genes was not ruled out (PP4). The variant has also been reported to segregate with LGMD in at least two affected family members from two nuclear Plain community families (PP1_Moderate; PMID: 9565988). The filtering allele frequency of this variant is 0.0002533 for South Asian exome chromosomes by gnomAD v2.1.1 (the upper threshold of the 95% CI of 3/30614), which is higher than the ClinGen LGMD VCEP threshold (<0.00009) for PM2_Supporting and therefore this criterion is not met. Expression of p.Arg91Cys in β-sarcoglycan in vitro has been shown to disrupt localization of the sarcoglycan complex to the plasma membrane, indicating an impact of the c.271C>T p.(Arg91Cys) variant on protein function (PMID: 37317968) (PS3_Moderate). The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to SGCB function (PP3). 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 1.0.0; 01/09/2025): PM3_Strong, PP4, PP1_Moderate, PS3_Moderate, PP3.

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least five individuals with signs of limb girdle muscular dystrophy, including in a homozygous state in families from the Plain community (0.5 pts; PMID: 35416532, 9565988) and confirmed in trans with a pathogenic variant in two cases (c.85A>T p.(Arg29Ter), 2.0 pts, PMID: 17994539, 11369190) (PM3_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to SGCB function (PP3).
PP4	✔	At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed severely reduced expression of β-sarcoglycan in skeletal muscle, which is highly specific for SGCB-related LGMD (PMID: 11369190); however, the presence of potentially diagnostic variants in all of the other three sarcoglycan genes was not ruled out (PP4).
PP1_Moderate	✔	The variant has been reported to segregate with LGMD in at least two affected family members from two nuclear Amish families (PP1_Moderate; PMID: 9565988). (capped with PP4_Strong)
PS3_Moderate	✔	Expression of p.Arg91Cys in β-sarcoglycan in vitro has been shown to disrupt localization of the sarcoglycan complex to the plasma membrane, indicating an impact of the c.271C>T p.(Arg91Cys) variant on protein function (PMID: 37317968) (PS3_Moderate). Qualitative immunofluorescence assay shows the sarcoglycan complex can still localize to the membrane when the variant is expressed in SGCB. PubMed:22095924

Not Met criteria codes

PM2	✖	The filtering allele frequency of this variant is 0.0002533 for South Asian exome chromosomes by gnomAD v2.1.1 (the upper threshold of the 95% CI of 3/30614), which is higher than the ClinGen LGMD VCEP threshold (<0.00009) for PM2_Supporting and therefore this criterion is not met.
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows