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Variant: NM_000232.5(SGCB):c.265G>A (p.Val89Met)

Version: 1.0

CA2918446

551805 (ClinVar)

Gene: SGCB (HGNC:6443)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: f98879f1-c7ae-43f8-9b74-3c53efca968b
Approved on: 2025/1/8
Published on: 2025/1/8

HGVS expressions

NM_000232.5:c.265G>A
NM_000232.5(SGCB):c.265G>A (p.Val89Met)
NC_000004.12:g.52029842C>T
CM000666.2:g.52029842C>T
NC_000004.11:g.52896008C>T
CM000666.1:g.52896008C>T
NC_000004.10:g.52590765C>T
NG_008891.1:g.13478G>A
ENST00000381431.10:c.265G>A
ENST00000381431.9:c.265G>A
ENST00000506357.5:c.348G>A
ENST00000514133.1:c.342G>A
NM_000232.4:c.265G>A

Likely Pathogenic

Met criteria codes 5

PP1 PP3 PP4 PM2_Supporting PM3_Strong

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 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.265G>A variant in SGCB is a missense variant predicted to cause substitution of valine by methionine at amino acid 89 (p.Val89Met). This variant has been detected in at least four individuals with symptoms of limb girdle muscular dystrophy. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (c.391C>T p.(Arg131Ter), 1 pt, ClinVar SCV000748307.5 internal data communication), and three patients were homozygous for the variant (1 pt, PMID: 28889091, 30838351, 29797799) (PM3_Strong). At least one of these patients displayed progressive limb girdle muscle weakness (PP4). This variant was also

shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 28889091; PP1). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the Admixed American population (1/34588 exome alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.932, which is above the threshold of 0.7, evidence that correlates with impact to SGCB 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 1.0.0; 01/08/2025): PM3_Strong, PP4, PM2_Supporting, PP3, PP1.

Met criteria codes

PP1	✔	This variant was shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 28889091).
PP3	✔	The computational predictor REVEL gives a score of 0.932, which is above the threshold of 0.7, evidence that correlates with impact to SGCB function (PP3).
PP4	✔	At least one patient with this variant and a second presumed diagnostic variant in SGCB displayed progressive limb girdle muscle weakness (PP4). ARC note: all SGC genes screened in Yis et al. patient but "deficient" provides insufficient detail about magnitude of reduction. Cannot confirm all SGC genes screened in GeneDx patient though it seems likely.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/34588 exome alleles) in the Admixed American population, which is lower than the ClinGen Limb-Girdle Muscular Dystrophy threshold (<0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM3_Strong	✔	This variant has been detected in at least four individuals with autosomal recessive limb girdle muscular dystrophy. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (c.391C>T p.(Arg131Ter), 1 pt, SCV000748307.5 internal data communication), and three patients were homozygous for the variant (1 pt, PMID: 28889091, 30838351, 29797799) (PM3_Strong).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000232.5(SGCB):c.265G>A (p.Val8...	Likely Pathogenic	Autosomal Recessive Limb-Girdle Muscular Dystrophy	2025-01-08	1.0	ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SGCB Version 1.0.0	SGCB

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