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Variant: NM_000023.4(SGCA):c.307A>G (p.Ile103Val)

Version: 1.0

CA8643746

284685 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5d050748-d2ab-4b4b-8322-305464b173d3
Approved on: 2026/4/29
Published on: 2026/5/7

HGVS expressions

NM_000023.4:c.307A>G
NM_000023.4(SGCA):c.307A>G (p.Ile103Val)
NC_000017.11:g.50167731A>G
CM000679.2:g.50167731A>G
NC_000017.10:g.48245092A>G
CM000679.1:g.48245092A>G
NC_000017.9:g.45600091A>G
NG_008889.1:g.6727A>G
ENST00000504073.2:c.307A>G
ENST00000511303.6:n.38-216A>G
ENST00000512526.2:c.303+4A>G
ENST00000682109.1:c.187A>G
ENST00000683226.1:n.17A>G
ENST00000683294.1:c.307A>G
ENST00000262018.8:c.307A>G
ENST00000262018.7:c.307A>G
ENST00000344627.10:c.307A>G
ENST00000502555.5:c.158-216A>G
ENST00000511303.5:c.34-216A>G
ENST00000512526.1:c.147+4A>G
ENST00000513821.5:c.307A>G
ENST00000513942.5:n.104-216A>G
ENST00000514934.1:c.*19-216A>G
NM_000023.2:c.307A>G
NM_001135697.1:c.307A>G
NM_000023.3:c.307A>G
NM_001135697.2:c.307A>G
NR_135553.1:n.363A>G
NM_001135697.3:c.307A>G
NR_135553.2:n.343A>G

Pathogenic

Met criteria codes 5

PP4_Strong | PM3_Strong | PM2_Supporting | PP1 | PP3

Not Met criteria codes 1

PS3

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.307A>G variant in SGCA is a missense variant predicted to cause substitution of isoleucine by valine at amino acid 103, p.(Ile103Val). This variant has been detected in five unrelated individuals with limb-girdle muscular dystrophy (PMID: 32528171, 30564623; Newcastle University, GRASP-LGMD Consortium internal data communication; LOVD SGCA_000155). Of those individuals, two were confirmed compound heterozygous for the variant and a pathogenic variant (c.229C>T p.(Arg77Cys), 1.0 pt, Newcastle University internal data communication; c.739G>A p.(Val247Met), 1.0 pt, PMID: 32528171, MYO-Seq study internal data communication). In at least three, individuals, the variant was reported in unconfirmed phase with a pathogenic variant (c.229C>T p.(Arg77Cys), 0.5 pts x2, PMID: 30564623, Newcastle University internal data communication; c.293G>A p.(Arg98His), 0.5 pts, PMID: 30564623, LOVD Individual #00219726) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic SGCA variant displayed progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Strong; PMID: 32528171). The variant has also been reported to segregate with autosomal recessive limb girdle muscular dystrophy in two affected siblings from one family (PP1; Newcastle University internal data communication). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000048072 (44/1176834 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion. The computational predictor REVEL gives a score of 0.826, 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 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, PM2_Supporting, PP1, PP3.

Met criteria codes

PP4_Strong ✔	At least one patient with this variant and a second presumed diagnostic SGCA variant displayed progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Strong; PMID: 32528171).
PM3_Strong ✔	This variant has been detected in five unrelated individuals with limb-girdle muscular dystrophy (PMID: 32528171, 30564623; Newcastle University, GRASP-LGMD Consortium internal data communication; LOVD SGCA_000155). Of those individuals, two were confirmed compound heterozygous for the variant and a pathogenic variant (c.229C>T p.(Arg77Cys), 1.0 pt, Newcastle University internal data communication; c.739G>A p.(Val247Met), 1.0 pt, PMID: 32528171, MYO-Seq study internal data communication). In at least three, individuals, the variant was reported in unconfirmed phase with a pathogenic variant (c.229C>T p.(Arg77Cys), 0.5 pts x2, PMID: 30564623, Newcastle University internal data communication; c.293G>A p.(Arg98His), 0.5 pts, PMID: 30564623, LOVD Individual #00219726) (PM3_Strong). this variant not present in gnomAD v2 so co-occurrence cannot be assessed
PM2_Supporting ✔	

The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000048072 (44/1176834 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, and therefore meets this criterion.

PP1	✔	The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in two affected siblings from one family (PP1; Newcastle University internal data communication).
PP3	✔	The computational predictor REVEL gives a score of 0.826, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3). Variant is the sixth nucleotide to the end of exon 3. SpliceAI: 0.190 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

Not Met criteria codes

PS3	✖	In an in vitro assay of membrane localization of the sarcoglycan complex, the Ile103Val protein had a functional score of -0.09, which is above the threshold to be considered damaging to this aspect of protein function (PS3_Moderate not met, Washington University internal data). In the Lek lab's assay, score of -0.8580317

Curation History

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