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_000023.4(SGCA):c.661C>T (p.Arg221Cys)

Version: 2.0

CA8643859

452720 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: e5736e98-a4d7-4384-bbb0-da1f2819c0d2
Approved on: 2025/10/28
Published on: 2025/11/11

HGVS expressions

NM_000023.4(SGCA):c.661C>T (p.Arg221Cys)
NM_000023.4:c.661C>T
NC_000017.11:g.50169168C>T
CM000679.2:g.50169168C>T
NC_000017.10:g.48246529C>T
CM000679.1:g.48246529C>T
NC_000017.9:g.45601528C>T
NG_008889.1:g.8164C>T
ENST00000504073.2:c.597+64C>T
ENST00000511303.6:n.309+596C>T
ENST00000512526.2:c.575+596C>T
ENST00000682109.1:c.541C>T
ENST00000683226.1:n.371C>T
ENST00000683294.1:c.661C>T
ENST00000262018.8:c.661C>T
ENST00000262018.7:c.661C>T
ENST00000344627.10:c.584+596C>T
ENST00000502555.5:c.*320C>T
ENST00000504073.1:c.64+64C>T
ENST00000511303.5:c.305+596C>T
ENST00000512526.1:c.419+596C>T
ENST00000513821.5:c.661C>T
ENST00000513942.5:n.375+596C>T
NM_000023.2:c.661C>T
NM_001135697.1:c.584+596C>T
NM_000023.3:c.661C>T
NM_001135697.2:c.584+596C>T
NR_135553.1:n.717C>T
NM_001135697.3:c.584+596C>T
NR_135553.2:n.697C>T

Likely Pathogenic

Met criteria codes 4

PM3_Strong PM5_Supporting PP3 PP4

Not Met criteria codes 21

PVS1 BS1 BS4 BS3 BS2 BP5 BP7 BP4 BP3 BP1 BP2 PM6 PM2 PS1 PS2 PS3 PS4 BA1 PM1 PM4 PP2

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.661C>T variant in SGCA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 221, p.(Arg221Cys). This variant has been identified in at least eight individuals with a clinical suspicion of limb girdle muscular dystrophy (PMID: 35416532, 28403181, 30564623, 32528171, 32875335; LOVD SGCA_000169; John Walton Muscular Dystrophy Research Centre internal data communication; ClinVar SCV000941635.5, SCV005198223.1 internal data communication), including confirmed in trans with the same pathogenic variant in two cases (c.229C>T p.(Arg77Cys), 1.0 pt x2, ClinVar SCV000941635.5, SCV005198223.1 internal data communication) (PP4, PM3_Strong). It has also been reported in a homozygous state in an individual undergoing clinical genome sequencing for suspected rare disease but without phenotype details provided (PMID: 33726816). The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003623 (33/91090 South Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold (0.00009) for PM2_Supporting (criterion not met). The computational predictor REVEL gives a score of 0.787, which is above the VCEP threshold of ≥0.70, evidence that correlates with impact to SGCA function (PP3). In addition, another missense variant at the same codon, c.662G>C p.(Arg221Pro), has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5_Supporting). 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; 10/28/2025): PP4, PM3_Strong, PP3, PM5_Supporting.

Met criteria codes

PM3_Strong ✔

This variant has been identified in at least eight individuals with a clinical suspicion of limb girdle muscular dystrophy (PMID: 35416532, 28403181, 30564623, 32528171, 32875335; LOVD SGCA_000169; John Walton Muscular Dystrophy Research Centre internal data communication; ClinVar SCV000941635.5, SCV005198223.1 internal data communication), including confirmed in trans with the same pathogenic variant in two cases (c.229C>T p.(Arg77Cys), 1.0 pt x2, ClinVar SCV000941635.5, SCV005198223.1 internal data communication) (PM3_Strong). It has also been reported in a homozygous state in an individual undergoing clinical genome sequencing for suspected rare disease but without phenotype details provided (PMID: 33726816). Ek et al. (2023) is cited in ClinVar, but I could not find this variant in the text or supplementary table. potential additional pts: 2 pts needed for Very Strong c.226C>T (p.Leu76Phe): unconfirmed phase, not on priority list; LP/P in ClinVar, at least 2 other lit reports (PMID: 24742800, 30345904) (0.5 pts if independently P) c.197T>A (p.Leu66His): unconfirmed phase, on priority list: P/LP/VUS in ClinVar, at least 2 other lit reports (PMID: 31069529, 33552634) (1.0 pt if independently P; 2 cases) p.(Arg34Cys): unconfirmed phase, independently LP (0.25 pts) c.488dup p.(Leu164ThrfsTer27): unconfirmed phase, not on priority list; expected P, at least 1 other lit report (PMID: 18996010) (0.5 pts if independently P) c.312G>A (p.Glu104=): unconfirmed phase, not on priority list; VUS in ClinVar, ablates canonical donor (PP3) (may stay VUS)

PM5_Supporting	✔	Another missense variant at the same codon, c.662G>C (p.Arg221Pro), has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.787, which is above the threshold of ≥0.70, evidence that correlates with impact to SGCA function (PP3).
PP4	✔	At least one patient with this variant and a second SGCA variant had a clinical suspicion of limb girdle muscular dystrophy (PP4). Alonso-Perez case has <30% protein expression but limited phenotype info and can't confidently confirm screening of other sarcoglycan genes.

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	Grpmax FAF 0.0002648
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2		✖	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003623 (33/91090 South Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold (0.00009) for PM2_Supporting (criterion not met).
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	Grpmax FAF 0.0002648
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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