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Variant: NM_000023.4(SGCA):c.100C>T (p.Arg34Cys)

Version: 1.0

CA210084

217250 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 34682e27-b411-4698-b6dc-d77b2b64b949
Approved on: 2025/1/9
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HGVS expressions

NM_000023.4(SGCA):c.100C>T (p.Arg34Cys)
NM_000023.4:c.100C>T
NC_000017.11:g.50167430C>T
CM000679.2:g.50167430C>T
NC_000017.10:g.48244791C>T
CM000679.1:g.48244791C>T
NC_000017.9:g.45599790C>T
NG_008889.1:g.6426C>T
ENST00000504073.2:c.100C>T
ENST00000511303.6:n.38-517C>T
ENST00000512526.2:c.100C>T
ENST00000682109.1:c.38-152C>T
ENST00000683294.1:c.100C>T
ENST00000262018.8:c.100C>T
ENST00000262018.7:c.100C>T
ENST00000344627.10:c.100C>T
ENST00000502555.5:c.100C>T
ENST00000511303.5:c.34-517C>T
ENST00000513821.5:c.100C>T
ENST00000513942.5:n.104-517C>T
ENST00000514934.1:c.159C>T
NM_000023.2:c.100C>T
NM_001135697.1:c.100C>T
NM_000023.3:c.100C>T
NM_001135697.2:c.100C>T
NR_135553.1:n.156C>T
NM_001135697.3:c.100C>T
NR_135553.2:n.136C>T

Likely Pathogenic

Met criteria codes 6

PP1 PP3 PM3_Supporting PP4_Strong PM2_Supporting PM5_Supporting

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 1.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000023.4: c.100C>T variant in SGCA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 34 (p.Arg34Cys). This variant has been reported in at least three patients with symptoms of limb girdle muscular dystrophy (PMID: 7663524, 21031578; Washington University internal clinic data communication), including in a homozygous state in one patient from a consanguineous family (0.25 pts) and confirmed in trans with a SGCA variant not yet curated by the VCEP and considered VUS (0.25 pts) (PM3_Supporting). At least one patient with this variant displayed progressive muscle weakness and significantly reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PP4_Strong; PMID: 7663524, 21031578, Washington University internal clinic data communication). The variant has also been reported to segregate with autosomal recessive limb girdle muscular dystrophy in one affected family member (PP1; PMID: 7663524). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000009 (1/113724 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LGMD VCEP threshold (0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting). Another missense variant at the same codon, c.101G>A (p.Arg34His), has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen 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 1.0.0; 01/09/2025): PM3_Supporting, PP4_Strong, PM5_Supporting, PP3, PM2_Supporting, PP1.

Met criteria codes

PP1	✔	The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in one affected family member (PP1; PMID: 7663524).
PP3	✔	The computational predictor REVEL gives a score of 0.809, which is above the threshold of 0.7, evidence that correlates with impact to SGCA function (PP3).
PM3_Supporting	✔	This variant has been reported in at least three patients with limb girdle muscular dystrophy (PMID: 7663524, 21031578; internal clinic data), including in a homozygous state in one patient from a consanguineous family (0.25 pts) and confirmed in trans with a SGCA variant not yet curated by the VCEP and considered VUS (0.25 pts) (PM3_Supporting).
PP4_Strong	✔	At least one patient with this variant displayed progressive muscle weakness and reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-associated autosomal recessive limb-girdle muscular dystrophy (PP4_Strong, PMIDs:7663524, 21031578, Internal contributor).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.000009 (1/113724 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LGMD VCEP threshold (0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM5_Supporting	✔	Another missense variant at the same codon, c.101G>A (p.Arg34His), has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PM5_Supporting).

Curation History

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