Variant: NM_000023.4(SGCA):c.229C>T (p.Arg77Cys)

Version: 1.0

CA120427

9437 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 932947fc-e18c-4bdf-a0d3-cd7109c13457
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HGVS expressions

NM_000023.4:c.229C>T
NM_000023.4(SGCA):c.229C>T (p.Arg77Cys)
NC_000017.11:g.50167653C>T
CM000679.2:g.50167653C>T
NC_000017.10:g.48245014C>T
CM000679.1:g.48245014C>T
NC_000017.9:g.45600013C>T
NG_008889.1:g.6649C>T
ENST00000504073.2:c.229C>T
ENST00000511303.6:n.38-294C>T
ENST00000512526.2:c.229C>T
ENST00000682109.1:c.109C>T
ENST00000683294.1:c.229C>T
ENST00000262018.8:c.229C>T
ENST00000262018.7:c.229C>T
ENST00000344627.10:c.229C>T
ENST00000502555.5:c.157+166C>T
ENST00000511303.5:c.34-294C>T
ENST00000512526.1:c.73C>T
ENST00000513821.5:c.229C>T
ENST00000513942.5:n.104-294C>T
ENST00000514934.1:c.*18+166C>T
NM_000023.2:c.229C>T
NM_001135697.1:c.229C>T
NM_000023.3:c.229C>T
NM_001135697.2:c.229C>T
NR_135553.1:n.285C>T
NM_001135697.3:c.229C>T
NR_135553.2:n.265C>T

Pathogenic

Met criteria codes 5

PM3_Strong PS3_Supporting PP3 PP4 PP1_Strong

Not Met criteria codes 21

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

BP4 BP3 BP1 BP2 BP5 BP7
PVS1 PS1 PS2 PS4 BA1
PP2 PM1 PM5 PM4 PM6
PM2 BS2 BS1 BS4 BS3

Evidence Links 0

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.229C>T variant in SGCA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 77 (p.Arg77Cys). This variant has been detected in at least 12 individuals with symptoms of limb girdle muscular dystrophy. Of those individuals, two were confirmed compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.850C>T, 2 pts, PMID: 12566530, LOVD Individual #0000223892), and at least two were homozygous for the variant (1 pt, PMID: 12566530, 23989969, 7663524, 37628638) (PM3_Strong). The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in 10 affected family members from five families (PP1_Strong; LOVD Individual #0000223892, PMID: 12566530, 7663524). At least one patient with this variant displayed progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PMID: 7663524; PP4) (capped with PP1_Strong). The filtering allele frequency of this variant is 0.0004392 (the lower threshold of the 95% CI of 62/112872 exome chromosomes) in the European (non-Finnish) population in gnomAD v2.1.1, which is lower than the ClinGen LGMD VCEP threshold (>0.0009) for BS1 (BS1, PM2_Supporting not met). In vitro assays have demonstrated this variant disrupts membrane localization of the sarcoglycan protein complex (PMID: 18535179; PS3_Supporting), and the computational predictor REVEL gives a score of 0.95, which exceeds the threshold of ≥0.70, 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 1.0.0; 01/08/2025): PM3_Strong, PP1_Strong, PP4, PP3, PS3_Supporting.

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least 12 individuals with autosomal recessive limb-girdle muscular dystrophy. Of those individuals, two were confirmed compound heterozygous for the variant and a pathogenic or likely pathogenic variant (c.850C>T, 2 pts, PMID: 12566530, LOVD). Ten patients were homozygous for the variant (1 pt, PMID: 12566530, 23989969, 7663524, 37628638) (PM3_Strong).
PS3_Supporting	✔	Confocal immunofluorescence in permeabilized βγδ-HEK cells showed the formation of intracellular aggregates by the R77C mutant, which does not localize with the other sarcoglycans and remains trapped in the Endoplasmic Reticulum (EM), indicating that this variant impacts protein function (PMID: 18535179) (PS3_supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.95, which exceeds the threshold of ≥0.70, evidence that correlates with impact to SGCA function (PP3).
PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness and reduced alpha-sarcoglycan protein expression, which is highly specific for SGCA-related LGMD (PMID: 7663524; PP4) (capped with PP1_Strong).
PP1_Strong	✔	The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in 10 affected family members from five families (PP1_Strong; LOVD, PMID: 12566530, 7663524).

Not Met criteria codes

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
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
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	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
PS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	✖	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
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM4		✖	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		✖	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
BS1		✖	The filtering allele frequency of this variant is 0.0004392 (the lower threshold of the 95% CI of 62/112872 exome chromosomes) in the European (non-Finnish) population in gnomAD v2.1.1, which is lower than the ClinGen LGMD VCEP threshold (>0.0009) for BS1 (BS1, PM2 not met).
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

Curation History

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