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Variant: NM_000023.4(SGCA):c.574C>T (p.Arg192Ter)

Version: 1.0

CA130100

37202 (ClinVar)

Gene: SGCA (HGNC:6442)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 073c5300-0c8f-44bc-9ace-d5159378c6a6
Approved on: 2025/1/7
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HGVS expressions

NM_000023.4(SGCA):c.574C>T (p.Arg192Ter)
NM_000023.4:c.574C>T
NC_000017.11:g.50168562C>T
CM000679.2:g.50168562C>T
NC_000017.10:g.48245923C>T
CM000679.1:g.48245923C>T
NC_000017.9:g.45600922C>T
NG_008889.1:g.7558C>T
ENST00000504073.2:c.574C>T
ENST00000511303.6:n.299C>T
ENST00000512526.2:c.565C>T
ENST00000682109.1:c.454C>T
ENST00000683226.1:n.284C>T
ENST00000683294.1:c.574C>T
ENST00000262018.8:c.574C>T
ENST00000262018.7:c.574C>T
ENST00000344627.10:c.574C>T
ENST00000502555.5:c.*233C>T
ENST00000504073.1:c.41C>T
ENST00000511303.5:c.295C>T
ENST00000512526.1:c.409C>T
ENST00000513821.5:c.574C>T
ENST00000513942.5:n.365C>T
ENST00000514934.1:c.*280C>T
NM_000023.2:c.574C>T
NM_001135697.1:c.574C>T
NM_000023.3:c.574C>T
NM_001135697.2:c.574C>T
NR_135553.1:n.630C>T
NM_001135697.3:c.574C>T
NR_135553.2:n.610C>T

Pathogenic

Met criteria codes 5

PP4 PM3 PP1_Strong PM2_Supporting PVS1

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Evidence Links 0

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.574C>T p.(Arg192Ter) variant in SGCA is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 5/10, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in four individuals with autosomal recessive limb girdle muscular dystrophy, all of whom were homozygous for the variant. Consanguinity was reported in one of the four families (1.0 pt, PMID: 26934379, 22303798; PM3). The variant has also been reported to co-segregate with autosomal recessive limb girdle muscular dystrophy in eight affected meioses from four families (PP1_Strong; PMID: 26934379, 22303798). At least one patient with this variant displayed progressive limb girdle muscle weakness and reduced expression of alpha-sarcoglycan protein in skeletal muscle, which is specific for SGCA-related LGMD (PP4; PMID: 26934379) (capped with PP1_Strong). The highest population minor allele frequency of this variant in gnomAD v2.1.1 is 0.00001 (1/71080 alleles) in the European (non-Finnish) population, which is lower than the VCEP threshold (0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting). 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; 01/07/2025): PVS1, PP1_Strong, PP4, PM3, PM2_Supporting.

Met criteria codes

PP4	✔	At least one patient with this variant displayed progressive weakness, myopathy on EMG, and reduced expression of encoded sarcoglycan protein complex in the muscle biopsy by IHC, which is highly specific for autosomal recessive limb-girdle muscular dystrophy (PP4; PMID: 26934379) (capped with PP1_Strong).
PM3	✔	This variant has been detected in 4 individuals with autosomal recessive limb-girdle muscular dystrophy. All individuals were homozygous for the variant. Three probands were reported to come from non consanguineous families and one family did report consanguinity (Max of 1 PM3 points awarded, PMIDs: 26934379, 22303798) (PM3).
PP1_Strong	✔	The variant has been reported to segregate with autosomal recessive limb girdle muscular dystrophy in 8 affected meioses from 4 families (PP1_Strong; PMID: 26934379, 22303798).
PM2_Supporting	✔	The highest population minor allele frequency of this variant in gnomAD v2.1.1 is 0.00001 (1/71080 alleles) in the European (non-Finnish) population, which is lower than the VCEP threshold (0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PVS1	✔	The NM_000023.4: c.574C>T p.(Arg192Ter) variant in SGCA is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 5/10, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Curation History

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