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Variant: NM_000232.5(SGCB):c.377_384dup (p.Gly129delinsGlnTer)

Version: 1.0

CA2918420

8714 (ClinVar)

Gene: SGCB (HGNC:6443)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 213e71e7-cd11-4a68-95a4-1ffff19be08c
Approved on: 2025/1/8
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HGVS expressions

NM_000232.5(SGCB):c.377_384dup (p.Gly129delinsGlnTer)
NM_000232.5:c.377_384dup
NC_000004.12:g.52029724_52029731dup
CM000666.2:g.52029724_52029731dup
NC_000004.11:g.52895890_52895897dup
CM000666.1:g.52895890_52895897dup
NC_000004.10:g.52590647_52590654dup
NG_008891.1:g.13590_13597dup
ENST00000381431.10:c.377_384dup
ENST00000381431.9:c.377_384dup
ENST00000506357.5:c.460_467dup
ENST00000514133.1:c.454_461dup
NM_000232.4:c.377_384dup

Pathogenic

Met criteria codes 5

PVS1 PP1_Moderate PP4_Moderate PM3_Strong PM2_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 SGCB 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_000232.5: c.377_384dup p.(Gly129delinsGlnTer) variant in SGCB, which is also known as p.(Gly129GlnfsTer2), is a presumed in tandem duplication of nucleotides 377-384, which is predicted to cause a frameshift and introduce a premature stop codon in biologically relevant exon 3/6, 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 at least 10 individuals with limb girdle muscular dystrophy, including in a homozygous state in four (1.0

pt) and confirmed in trans with a likely pathogenic or pathogenic variant in two (c.699_702del, 1.0 pt; c.85A>T p.(Arg29Ter), 1.0 pt) (PMID: 25862795, 36077211, 10662809; PM3_Strong). This variant has been reported to segregate with autosomal recessive LGMD in two affected family members from two Italian families (PMID: 25862795; PP1_Moderate). At least one patient with this variant and a second SGCB variant showed a progressive LGMD phenotype and significantly reduced expression of beta-sarcoglycan in skeletal muscle, which is highly specific for SGCB-related LGMD (PP4_Moderate (capped with PP1_Moderate); PMID: 36077211). The highest minor allele frequency of this variant is 0.000008791 in the European (non-Finnish) population in gnomAD v2.1.1 (1/113750 exome chromosomes), which is lower than the LGMD 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; 01/08/2025): PVS1, PM3_Strong, PP1_Moderate, PP4_Moderate, PM2_Supporting.

Met criteria codes

PVS1	✔	The NM_000232.5: c.377_384dup p.(Gly129GlnfsTer2) variant in SGCB is a duplication of nucleotides 377-384 predicted to cause a frameshift and premature stop codon in biologically relevant exon 3/6, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PP1_Moderate	✔	This variant has been reported to segregate with autosomal recessive LGMD in two affected family members from two Italian families (PMID: 25862795). ARC note: Semplicini et al. (2015) supplementary table shows 2 pairs of homozygous siblings (3 & 4, 9 & 16.
PP4_Moderate	✔	At least one patient with this variant showed a progressive LGMD phenotype and significantly reduced expression of β-sarcoglycan in skeletal muscle, which is highly specific for SGCB-related LGMD (PP4_Moderate (capped with PP1); PMID: 36077211). ARC: cannot confirm screening of all SGC genes in Semplicini patients. Magri et al. patient had a panel test and <30% normal expression of all 4 SGC genes.
PM3_Strong	✔	This variant has been detected in at least 10 individuals with limb girdle muscular dystrophy, including in a homozygous state in four (1.0 pt) and confirmed in trans with a likely pathogenic or pathogenic variant in two (c.699_702del, 1.0 pt; c.85A>T p.(Arg29Ter), 1.0 pt); (PMID: 25862795, 36077211, 10662809; PM3_Strong). ARC: Semplicini et al. report 3 homozygous probands (2 consang, 1 not; (1.0 pt) and 3 compound hets: c.699_702del (1.0 pt), c.552T>G p.(Tyr184Ter) (uncurated), c.85A>T p.(Arg29Ter) (1.0 pt). c.243+3_243+6del and c.243+1548T>C uncurated Overall: 4 hom: 2 consang (0.25 x2), 2 non-consang (0.5 x2) = 1 pt 6 comp het, with 2 confirmed LP/P = 2 pt
PM2_Supporting	✔	The minor allele frequency of this variant is 0.000008791 in the European (non-Finnish) population in gnomAD v2.1.1 (1/113750 exome chromosomes), which is lower than the LGMD VCEP threshold (<0.00009) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows

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