

Variant: NM_001130987.2(DYSF):c.3085+2T>C

Version: 1.0

CA10604913 [↗](#)

284804 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 3ab21351-9e54-47f3-a8eb-614abd757f5f

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HGVS expressions

NM_001130987.2:c.3085+2T>C

NM_001130987.2(DYSF):c.3085+2T>C

NC_000002.12:g.71570336T>C

CM000664.2:g.71570336T>C

NC_000002.11:g.71797466T>C

CM000664.1:g.71797466T>C

NC_000002.10:g.71650974T>C

NG_008694.1:g.121714T>C

ENST00000698057.1:c.457+2T>C

ENST00000258104.8:c.3031+2T>C

ENST00000410020.8:c.3085+2T>C

ENST00000258104.7:c.3031+2T>C

ENST00000394120.6:c.3034+2T>C

ENST00000409366.5:c.3034+2T>C

ENST00000409582.7:c.3082+2T>C

ENST00000409651.5:c.3127+2T>C

ENST00000409744.5:c.2992+2T>C

ENST00000409762.5:c.3082+2T>C

ENST00000410020.7:c.3085+2T>C

ENST00000410041.1:c.3085+2T>C

ENST00000413539.6:c.3124+2T>C

ENST00000429174.6:c.3031+2T>C

ENST00000461565.1:n.197+2T>C

NM_001130455.1:c.3034+2T>C

NM_001130976.1:c.2989+2T>C

NM_001130977.1:c.2989+2T>C

NM_001130978.1:c.3031+2T>C

NM_001130979.1:c.3124+2T>C

NM_001130980.1:c.3082+2T>C

NM_001130981.1:c.3082+2T>C

NM_001130982.1:c.3127+2T>C

NM_001130983.1:c.3034+2T>C

NM_001130984.1:c.2992+2T>C

NM_001130985.1:c.3085+2T>C

NM_001130986.1:c.2992+2T>C

NM_001130987.1:c.3085+2T>C

NM_003494.3:c.3031+2T>C

NM_001130455.2:c.3034+2T>C
NM_001130976.2:c.2989+2T>C
NM_001130977.2:c.2989+2T>C
NM_001130978.2:c.3031+2T>C
NM_001130979.2:c.3124+2T>C
NM_001130980.2:c.3082+2T>C
NM_001130981.2:c.3082+2T>C
NM_001130982.2:c.3127+2T>C
NM_001130983.2:c.3034+2T>C
NM_001130984.2:c.2992+2T>C
NM_001130985.2:c.3085+2T>C
NM_001130986.2:c.2992+2T>C
NM_003494.4:c.3031+2T>C

Pathogenic

Met criteria codes 5

PM3 PP1_Strong PVS1
PM2_Supporting PP4

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 DYSF 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_003494.4: c.3031+2T>C variant in DYSF, which is also known as NM_001130987.2: c.3085+2T>C, occurs within the canonical splice donor site (+/- 1,2) of intron 28. SpliceAI gives a delta score of 0.92 for loss of the canonical donor. RNAseq analysis has demonstrated that this variant causes skipping of exon 28, resulting in a frameshift and premature truncation, p.Asn976AlafsTer46 (PMID: 36983702; PVS1_RNA). This variant has been reported in at least six patients with clinical features consistent with LGMD, including in a homozygous state (0.5 pts) and confirmed in trans with a pathogenic variant (NM_003494.4: c.855+1del, 1.0 pt) (PMID: 26444858, 36983702, 18853459; PM3). At least one individual with this variant and a second DYSF variant had a clinical phenotype considered consistent with LGMD (PMID: 18853459; PP4). In addition, this variant has been shown to co-segregate with autosomal recessive LGMD in at least four family members from three families (PMID: 26444858, 18853459; PP1_Strong). Haplotype analysis of three seemingly unrelated families from Central Switzerland confirmed a founder effect of this variant in that region. The highest population allele frequency of this variant is in gnomAD v4.1.0 is 8.476e-7 (1/1179858 European (non-Finnish) alleles), which is less than the LGMD VCEP threshold for PM2_Supporting (0.0001), 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; 07/29/2025): PVS1_RNA, PM3, PP4, PP1_Strong, PM2_Supporting.

Met criteria codes

PM3



This variant has been reported in at least six patients with clinical features consistent with LGMD, including in a homozygous state (0.5 pts) and confirmed in trans with a pathogenic variant (NM_003494.4: c.855+1del, 1.0 pt) (PMID: 26444858, 36983702, 18853459; PM3).

PP1_Strong			This variant has been shown to co-segregate with autosomal recessive LGMD in at least four family members from three families (PMID: 26444858, 18853459; PP1_Strong). Haplotype analysis of three seemingly unrelated families from Central Switzerland confirmed a founder effect of this variant in that region.
PVS1			The NM_003494.4: c.3031+2T>C variant in DYSF, which is also known as NM_001130987.2: c.3085+2T>C, occurs within the canonical splice donor site (+/- 1,2) of intron 28. RNAseq analysis has demonstrated that this variant causes skipping of exon 28, resulting in a frameshift and premature truncation, p.Asn976AlafsTer46 (PMID: 36983702; PVS1_RNA). SpliceAI: delta score 0.92 for loss of canonical donor (ref 0.99, alt 0.07) delta score 0.39 for gain of cryptic donor at +59 (ref 0.02, alt 0.42) exon skipping due to loss of canonical donor would be out of frame use of cryptic donor at +59 would be out of frame GENEie: uncertain (because same sequence variants in other gene LB in ClinVar) mean NIF impact -96% (alt mean NIF 0.03) skipping of exon 28 is most common splice error in SpliceVault (3694 samples) cryptic donor at +59 is used in 95 samples
PM2_Supporting			The highest population allele frequency of this variant is in gnomAD v4.1.0 is 8.476e-7 (1/1179858 European (non-Finnish) alleles), which is less than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting).
PP4			This variant has been reported in conjunction with a second DYSF variant in at least one individual with a clinical phenotype considered consistent with LGMD (PMID: 18853459; PP4).

Curation History 		
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