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Variant: NM_003494.4:c.3031G>C

Version: 1.0

CA347216867

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: c3a6675d-60b5-47c8-9a29-98000a3aa6c2
Approved on: 2025/8/26
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HGVS expressions

NM_003494.4:c.3031G>C
NC_000002.12:g.71570334G>C
CM000664.2:g.71570334G>C
NC_000002.11:g.71797464G>C
CM000664.1:g.71797464G>C
NC_000002.10:g.71650972G>C
NG_008694.1:g.121712G>C
ENST00000698057.1:c.457G>C
ENST00000258104.8:c.3031G>C
ENST00000410020.8:c.3085G>C
ENST00000258104.7:c.3031G>C
ENST00000394120.6:c.3034G>C
ENST00000409366.5:c.3034G>C
ENST00000409582.7:c.3082G>C
ENST00000409651.5:c.3127G>C
ENST00000409744.5:c.2992G>C
ENST00000409762.5:c.3082G>C
ENST00000410020.7:c.3085G>C
ENST00000410041.1:c.3085G>C
ENST00000413539.6:c.3124G>C
ENST00000429174.6:c.3031G>C
ENST00000461565.1:n.197G>C
NM_001130455.1:c.3034G>C
NM_001130976.1:c.2989G>C
NM_001130977.1:c.2989G>C
NM_001130978.1:c.3031G>C
NM_001130979.1:c.3124G>C
NM_001130980.1:c.3082G>C
NM_001130981.1:c.3082G>C
NM_001130982.1:c.3127G>C
NM_001130983.1:c.3034G>C
NM_001130984.1:c.2992G>C
NM_001130985.1:c.3085G>C
NM_001130986.1:c.2992G>C
NM_001130987.1:c.3085G>C
NM_003494.3:c.3031G>C
NM_001130987.2:c.3085G>C

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

Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Strong PM2_Supporting PVS1_Strong

Not Met criteria codes 1

PS1

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.3031G>C variant in DYSF, which is also known as NM_001130987.2: c.3085G>C p.(Gly1029Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 1011, p.(Gly1011Arg). This variant affects the last nucleotide of exon 28, and RNAseq analysis has demonstrated two different splice effects: inclusion of intron 28 and skipping of exon 28. Both of these events result in a frameshift and premature truncation for which nonsense mediated decay is expected; however, the possibility of retention of some degree of constitutive splicing was not ruled out (PVS1_Strong_RNA). This variant has been observed in unknown phase with a pathogenic variant in one patient with features consistent with LGMD (NM_003494.4: c.855+1del, 0.5 pts, PMID: 36983702; PM3_Supporting). This patient had a clinical diagnosis of LGMD and absent dysferlin protein expression by immunohistochemistry and western blot of skeletal muscle (PMID: 36983702, 33610434; PP4_Strong). This variant is absent from gnomAD v4.1.0 (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; 08/26/2025): PVS1_Strong_RNA, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been observed in unknown phase with a pathogenic variant in one patient with features consistent with LGMD (NM_003494.4: c.855+1del, 0.5 pts, PMID: 36983702; PM3_Supporting). cannot check co-occurrence data
PP4_Strong	✔	This patient had a clinical diagnosis of LGMD and absent dysferlin protein expression by immunohistochemistry and western blot of skeletal muscle (PMID: 36983702, 33610434; PP4_Strong).

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PVS1_Strong	✔	The NM_003494.4: c.3031G>C variant in DYSF, which is also known as NM_001130987.2: c.3085G>C p.(Gly1029Arg), is a missense variant predicted to cause substitution of glycine by arginine at amino acid 1011, p.(Gly1011Arg). This variant affects the last nucleotide of exon 28, and RNAseq analysis has demonstrated two different splice effects: inclusion of intron 28 and skipping of exon 28. Both of these events result in a frameshift and premature truncation for which nonsense mediated decay is expected; however, the possibility of retention of some degree of constitutive splicing was not ruled out (PVS1_Strong_RNA). SpliceAI: 0.9 for loss of annotated donor (alt 0.09) 0.44 for gain of alternative donor in the intron at +59 (alt 0.46) GENEie: 99.9% probability splice-altering 3 NIF stars: mean NIF impact -98% but no NIF 0 window SpliceVAULT top 3 are all out of frame: skipping of exon 28 (3,694 samples) and use of 2 cryptic donors: +59 (95 samples), +158 (34 samples) RNAseq: inclusion of entire intron 28, resulting in p.Gly1011Argfs (new stop codon 120 bp into the inserted intron 28) skipping of exon 28, resulting in p.Asn976AlafsX46 quantification not done: 40% intron retention, 8% exon skipping, 52% ref Downgrading to PVS1_Strong_RNA would not change P classification

Not Met criteria codes

PS1	✖	Another nucleotide change affecting the same splice donor site and with the same predicted and experimentally demonstrated splice effect, NM_003494.4: c.3031+2T>C, is classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (PS1_Supporting). Curated variant: SpliceAI 0.9 for donor loss (p-score 0.09) and 0.44 (p-score 0.46) for gain of alternative donor into the intron at +59 GENEie: 99.9% probability splice-altering 3 NIF stars: mean NIF impact -98% but no NIF 0 window 3 similar impact variants: c.3085+1G>T, c.3085+1G>A, c.3085+2T>C SpliceVAULT top 3 are all out of frame: skipping of exon 28 and use of 2 cryptic donors RNAseq data showed two different splice effects: 1) inclusion of the entire DYSF intron 28 which results in a frameshift and the presence of a premature stop codon 120bp into the inserted intron, p.Gly1011Argfs; 2) complete skipping of exon 28, r.2926_3031del, resulting in a frameshift and premature truncation, p.Asn976AlafsX46. NMD expected for both of these events. Comparison variant c.3031+2T>C SpliceAI 0.92 for donor loss (alt 0.07) and 0.39 (alt 0.42) for gain of alternative donor into the intron at +59 GENEie: Uncertain (another variant causing the same sequence change in another gene called LB but without evidence) 2 NIF stars: mean NIF impact -96% but no NIF 0 window 2 similar impact variants: c.3085+1G>T, c.3085+1G>A. Note that the curated variant is not yet in ClinVar and so I believe was not eligible as a similar impact variant. SpliceVAULT top 3 are all out of frame: skipping of exon 28 and use of 2 cryptic donors shown by RNAseq to cause skipping of exon 28, resulting in a frameshift and premature truncation Similar SpliceAI scores, same experimentally demonstrated consequence of exon skipping resulting in NMD but curated variant had additional effect of intron retention (also resulting in NMD so same functional consequence). Comparison variant located within same splice region and at +/-1,2 dinucleotide position and classified as P (PVS1_RNA, PM3, PP4, PP1_Strong, PM2_Supporting). if computational code applicable to curated variant is PVS1_RNA, PS1_Supporting if computational code applicable to curated variant is PVS1_Strong, _Moderate, or _Supporting _RNA, PS1 Per VCEP discussion, could probably apply given same functional consequence of splice effects, but P classification already reached. polyA (adenylated transcripts only) vs ribosomal depleted total RNA

Curation History

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