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Variant: NM_001130987.2(DYSF):c.1274_1276+4dup

Version: 1.0

CA1705669

497131 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 43b1324a-d892-4f96-933f-2aa736c2f75b
Approved on: 2026/3/23
Published on: 2026/4/10

HGVS expressions

NM_001130987.2:c.1274_1276+4dup
NM_001130987.2(DYSF):c.1274_1276+4dup
NC_000002.12:g.71526344_71526350dup
CM000664.2:g.71526344_71526350dup
NC_000002.11:g.71753474_71753480dup
CM000664.1:g.71753474_71753480dup
NC_000002.10:g.71606982_71606988dup
NG_008694.1:g.77722_77728dup
ENST00000258104.8:c.1178_1180+4dup
ENST00000410020.8:c.1274_1276+4dup
ENST00000258104.7:c.1178_1180+4dup
ENST00000394120.6:c.1181_1183+4dup
ENST00000409366.5:c.1181_1183+4dup
ENST00000409582.7:c.1271_1273+4dup
ENST00000409651.5:c.1274_1276+4dup
ENST00000409744.5:c.1181_1183+4dup
ENST00000409762.5:c.1271_1273+4dup
ENST00000410020.7:c.1274_1276+4dup
ENST00000410041.1:c.1274_1276+4dup
ENST00000413539.6:c.1271_1273+4dup
ENST00000429174.6:c.1178_1180+4dup
NM_001130455.1:c.1181_1183+4dup
NM_001130976.1:c.1178_1180+4dup
NM_001130977.1:c.1178_1180+4dup
NM_001130978.1:c.1178_1180+4dup
NM_001130979.1:c.1271_1273+4dup
NM_001130980.1:c.1271_1273+4dup
NM_001130981.1:c.1271_1273+4dup
NM_001130982.1:c.1274_1276+4dup
NM_001130983.1:c.1181_1183+4dup
NM_001130984.1:c.1181_1183+4dup
NM_001130985.1:c.1274_1276+4dup
NM_001130986.1:c.1181_1183+4dup
NM_001130987.1:c.1274_1276+4dup
NM_003494.3:c.1178_1180+4dup
NM_001130455.2:c.1181_1183+4dup
NM_001130976.2:c.1178_1180+4dup

NM_001130977.2:c.1178_1180+4dup
NM_001130978.2:c.1178_1180+4dup
NM_001130979.2:c.1271_1273+4dup
NM_001130980.2:c.1271_1273+4dup
NM_001130981.2:c.1271_1273+4dup
NM_001130982.2:c.1274_1276+4dup
NM_001130983.2:c.1181_1183+4dup
NM_001130984.2:c.1181_1183+4dup
NM_001130985.2:c.1274_1276+4dup
NM_001130986.2:c.1181_1183+4dup
NM_003494.4:c.1178_1180+4dup

Likely Pathogenic

Met criteria codes 1

PVS1

Not Met criteria codes 6

PM2 PM3 BS1 BP7 PP3 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 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.1178_1180+4dup variant in DYSF, which is also known as NM_001130987.2: c.1274_1276+4dup, is a duplication of 7 nucleotides spanning the boundary between exon 12 and intron 12, causing exon 12 to be extended by 7 bp and introducing a frameshift and premature truncation, p.(Met394SerfsTer20), with nonsense mediated decay expected (PVS1). While the GT at the original +1,2 position is maintained in the presence of the duplication, the splice donor at the original exon-intron boundary is not expected to be used because it is ablated by the duplication-induced replacement of GT with AG at the original +5,6 position. This variant has been observed in a heterozygous state in two patients with a clinical suspicion of LGMD or other muscular dystrophy, including one with a complete absence of dysferlin immunostaining in skeletal muscle. However, no second allele was identified in either case (PMID: 18832576, 30564623; LOVD Individual 00222254) (PM3_Supporting and PP4 not met). The upper threshold of the 95% CI of the Grpmax variant allele frequency is 0.0001051 in gnomAD v4.1.0 (3/73748 African/African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (<0.0001) (PM2_Supporting not met). In summary, this variant meets criteria to be classified as Likely pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications version 2.0.0; 03/23/2026): PVS1.

Met criteria codes

PVS1	✔	The NM_003494.4: c.1178_1180+4dup variant in DYSF, which is also known as NM_001130987.2: c.1274_1276+4dup, is a duplication of 7 nucleotides spanning the boundary between exon 12 and intron 12, causing exon 12 to be extended by 7 bp and resulting in a frameshift and premature truncation, p.(Met394SerfsTer20), with nonsense mediated decay expected (PVS1). While the GT is maintained at the original +1,2 dinucleotide positions in the presence of the duplication, the dup alters the sequence at the original exon-intron boundary via replacement of the GT at the +5/6 position with AG. This alteration completely ablates the splice donor site at the original exon-

intron boundary (GENEie gives 3 NIF 0 windows). The now-shifted splice donor sequence following the extended exon is thus expected to be used, shifting the reading frame and introducing a PTC. VEP annotates this variant as a frameshift (see gnomAD).

Not Met criteria codes

PM2	✖	The upper threshold of the 95% CI of the Grpmax variant allele frequency is 0.0001051 in gnomAD v4.1.0 (3/73748 African/African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_Supporting (<0.0001).
PM3	✖	This variant has been observed in a heterozygous state in two patients with a clinical suspicion of LGMD or muscular dystrophy, including one with a complete absence of dysferlin immunostaining in skeletal muscle. However, no second allele was identified in either case (PMID: 18832576, 30564623; LOVD Individual 00222254) (PM3 not met).
BS1	✖	The Grpmax FAF (the lower bound of the 95% confidence interval of the maximum credible genetic ancestry group allele frequency) is 0.00001009, which is less than the ClinGen LGMD VCEP threshold for BS1 (>0.001)
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	PVS1 applied
PP4	✖	Only observed as a single hit

Curation History

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