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Variant: NM_001130987.2(DYSF):c.1273C>T (p.Gln425Ter)

Version: 1.0

CA347213670

429885 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: cea3f16a-8c8c-4dcd-844b-2888928e487a
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2:c.1273C>T
NM_001130987.2(DYSF):c.1273C>T (p.Gln425Ter)
NC_000002.12:g.71526343C>T
CM000664.2:g.71526343C>T
NC_000002.11:g.71753473C>T
CM000664.1:g.71753473C>T
NC_000002.10:g.71606981C>T
NG_008694.1:g.77721C>T
ENST00000258104.8:c.1177C>T
ENST00000410020.8:c.1273C>T
ENST00000258104.7:c.1177C>T
ENST00000394120.6:c.1180C>T
ENST00000409366.5:c.1180C>T
ENST00000409582.7:c.1270C>T
ENST00000409651.5:c.1273C>T
ENST00000409744.5:c.1180C>T
ENST00000409762.5:c.1270C>T
ENST00000410020.7:c.1273C>T
ENST00000410041.1:c.1273C>T
ENST00000413539.6:c.1270C>T
ENST00000429174.6:c.1177C>T
NM_001130455.1:c.1180C>T
NM_001130976.1:c.1177C>T
NM_001130977.1:c.1177C>T
NM_001130978.1:c.1177C>T
NM_001130979.1:c.1270C>T
NM_001130980.1:c.1270C>T
NM_001130981.1:c.1270C>T
NM_001130982.1:c.1273C>T
NM_001130983.1:c.1180C>T
NM_001130984.1:c.1180C>T
NM_001130985.1:c.1273C>T
NM_001130986.1:c.1180C>T
NM_001130987.1:c.1273C>T
NM_003494.3:c.1177C>T
NM_001130455.2:c.1180C>T
NM_001130976.2:c.1177C>T

NM_001130977.2:c.1177C>T
NM_001130978.2:c.1177C>T
NM_001130979.2:c.1270C>T
NM_001130980.2:c.1270C>T
NM_001130981.2:c.1270C>T
NM_001130982.2:c.1273C>T
NM_001130983.2:c.1180C>T
NM_001130984.2:c.1180C>T
NM_001130985.2:c.1273C>T
NM_001130986.2:c.1180C>T
NM_003494.4:c.1177C>T

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1 PP4_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 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.1177C>T p.(Glu393Ter) variant in DYSF, which is also known as NM_001130987.2: c.1273C>T p.(Gln425Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 12/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been identified with a second DYSF variant in at least three unrelated individuals with features consistent with LGMD (PMID: 18853459, 33610434; LOVD DYSF_000044), including in unconfirmed phase with a pathogenic variant (NM_003494.4: c.1180+5G>A, 0.5 pts, LOVD Individual #00215246; PM3_Supporting). At least one patient with this variant and a second presumed diagnostic DYSF variant had both a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 33610434). The highest population allele frequency of this variant in gnomAD v.1.0 is 0.00001352 (1/73984 African/African American chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) (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, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been identified with a second DYSF variant in at least three unrelated individuals with features consistent with LGMD (PMID: 18853459, 33610434; LOVD DYSF_000044), including in unconfirmed phase with a pathogenic variant (NM_003494.4: c.1180+5G>A, 0.5 pts, LOVD Individual #00215246; PM3_Supporting). c.1180+5G>A is P without evidence from this case, predicted on a different haplotype from the curated variant
PVS1	✔	The NM_003494.4: c.1177C>T p.(Glu393Ter) variant in DYSF, which is also known as NM_001130987.2: c.1273C>T p.(Gln425Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 12/55,

leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 33610434). PMID: 33610434 Moore et al. (2021) patient 162: LGMDR2 clinical diagnosis, absent dysferlin expression in skeletal muscle by IHC and WB. c.1177C>T p.(Glu393Ter) in unknown phase with c.1168G>T p.(Asp390Tyr), which is not yet curated and is not in ClinVar but is absent from gnomAD v4 (BA1, BS1 not applicable).
PM2_Supporting	✔	The highest population allele frequency of this variant in gnomAD v.1.0 is 0.00001352 (1/73984 African/African American chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) (PM2_Supporting). PM2_Supporting also met with FAF from European (non-Finnish) exome chromosomes 0.000011841 (the upper threshold of the 95% CI of 7/1110352)

Curation History

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