The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001130987.2(DYSF):c.1888C>T (p.Gln630Ter)

Version: 1.0

CA277606

217223 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8b27314b-e17b-4a59-978b-7f6c0d3b23f9
Approved on: 2025/9/30
Published on: 2025/10/9

HGVS expressions

NM_001130987.2(DYSF):c.1888C>T (p.Gln630Ter)
NM_001130987.2:c.1888C>T
NC_000002.12:g.71553092C>T
CM000664.2:g.71553092C>T
NC_000002.11:g.71780222C>T
CM000664.1:g.71780222C>T
NC_000002.10:g.71633730C>T
NG_008694.1:g.104470C>T
ENST00000258104.8:c.1834C>T
ENST00000410020.8:c.1888C>T
ENST00000258104.7:c.1834C>T
ENST00000394120.6:c.1837C>T
ENST00000409366.5:c.1837C>T
ENST00000409582.7:c.1885C>T
ENST00000409651.5:c.1930C>T
ENST00000409744.5:c.1795C>T
ENST00000409762.5:c.1885C>T
ENST00000410020.7:c.1888C>T
ENST00000410041.1:c.1888C>T
ENST00000413539.6:c.1927C>T
ENST00000429174.6:c.1834C>T
NM_001130455.1:c.1837C>T
NM_001130976.1:c.1792C>T
NM_001130977.1:c.1792C>T
NM_001130978.1:c.1834C>T
NM_001130979.1:c.1927C>T
NM_001130980.1:c.1885C>T
NM_001130981.1:c.1885C>T
NM_001130982.1:c.1930C>T
NM_001130983.1:c.1837C>T
NM_001130984.1:c.1795C>T
NM_001130985.1:c.1888C>T
NM_001130986.1:c.1795C>T
NM_001130987.1:c.1888C>T
NM_003494.3:c.1834C>T
NM_001130455.2:c.1837C>T
NM_001130976.2:c.1792C>T

NM_001130977.2:c.1792C>T
NM_001130978.2:c.1834C>T
NM_001130979.2:c.1927C>T
NM_001130980.2:c.1885C>T
NM_001130981.2:c.1885C>T
NM_001130982.2:c.1930C>T
NM_001130983.2:c.1837C>T
NM_001130984.2:c.1795C>T
NM_001130985.2:c.1888C>T
NM_001130986.2:c.1795C>T
NM_003494.4:c.1834C>T

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PM3 PP4_Strong

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.1834C>T p.(Gln612Ter) variant in DYSF, which is also known as NM_001130987.2: c.1888C>T p.(Gln630Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 20/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been identified in at least seven individuals with dysferlinopathy (PMID: 11053681, 18832576, 18853459, 21522182, 25493284, 36983702), including in unconfirmed phase with a pathogenic variant in two patients (NM_003494.4: c.5768-51_5946+50del (exon 52 deletion), 0.5 pts, PMID: 36983702; NM_003494.4: c.4886+1249G>T, 0.5 pts, PMID: 25493284) (PM3). At least one individual with two presumed diagnostic DYSF variants displayed slow progressive muscle weakness and reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 18832576, 18853459, 21522182, 25493284, 36983702; PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000028602 (based on 24/1180048 European (non-Finnish) chromosomes), which is less than the ClinGen 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 2.0.0; 09/30/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000028602 (based on 24/1180048 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PVS1	✔	The NM_003494.4: c.1834C>T p.(Gln612Ter) variant in DYSF, which is also known as NM_001130987.2: c.1888C>T p.(Gln630Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 20/55,

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

PM3	✔	This variant has been identified in at least seven individuals with dysferlinopathy (PMID: 11053681, 18832576, 18853459, 21522182, 25493284, 36983702), including in unconfirmed phase with a pathogenic variant in two patients (NM_003494.4: c.5768-51_5946+50del (exon 52 deletion), 0.5 pts, PMID: 36983702; NM_003494.4: c.4886+1249G>T, 0.5 pts, PMID: 25493284) (PM3). Cannot check co-occurrence in gnomAD v2 for either variant
PP4_Strong	✔	At least one individual with two presumed diagnostic DYSF variants displayed slow progressive muscle weakness and reduced or absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 18832576, 18853459, 21522182, 25493284, 36983702; PP4_Strong).

Curation History

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