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.5298del (p.Glu1766fs)

Version: 1.0

CA2573135907

1455030 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7e3805af-ba9f-478e-961f-9385ace168f2
Approved on: 2025/2/25
Published on: 2025/3/7

HGVS expressions

NM_001130987.2(DYSF):c.5298del (p.Glu1766fs)
NM_001130987.2:c.5298del
NC_000002.12:g.71665285del
CM000664.2:g.71665285del
NC_000002.11:g.71892415del
CM000664.1:g.71892415del
NC_000002.10:g.71745923del
NG_008694.1:g.216663del
ENST00000698057.1:c.2712del
ENST00000698058.1:c.1929del
ENST00000698059.1:c.2037del
ENST00000258104.8:c.5181del
ENST00000410020.8:c.5298del
ENST00000258104.7:c.5181del
ENST00000394120.6:c.5184del
ENST00000409366.5:c.5247del
ENST00000409582.7:c.5295del
ENST00000409651.5:c.5277del
ENST00000409744.5:c.5205del
ENST00000409762.5:c.5232del
ENST00000410020.7:c.5298del
ENST00000410041.1:c.5235del
ENST00000413539.6:c.5274del
ENST00000429174.6:c.5244del
ENST00000479049.6:n.2066del
NM_001130455.1:c.5184del
NM_001130976.1:c.5139del
NM_001130977.1:c.5202del
NM_001130978.1:c.5244del
NM_001130979.1:c.5274del
NM_001130980.1:c.5232del
NM_001130981.1:c.5295del
NM_001130982.1:c.5277del
NM_001130983.1:c.5247del
NM_001130984.1:c.5205del
NM_001130985.1:c.5235del
NM_001130986.1:c.5142del

NM_001130987.1:c.5298del
NM_003494.3:c.5181del
NM_001130455.2:c.5184del
NM_001130976.2:c.5139del
NM_001130977.2:c.5202del
NM_001130978.2:c.5244del
NM_001130979.2:c.5274del
NM_001130980.2:c.5232del
NM_001130981.2:c.5295del
NM_001130982.2:c.5277del
NM_001130983.2:c.5247del
NM_001130984.2:c.5205del
NM_001130985.2:c.5235del
NM_001130986.2:c.5142del
NM_003494.4:c.5181del

Pathogenic

Met criteria codes 4

PVS1 PM3 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.5181del p.(Glu1727AspfsTer7) variant in DYSF, which is also known as NM_001130987.2: c.5298del (p.Glu1766AspfsTer7), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 46/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been reported in at least two individuals with clinical signs of limb girdle muscular dystrophy, including in a homozygous state (0.5 pts, PMID: 29970176) and confirmed in trans with a likely pathogenic or pathogenic variant (c.1668_1669insGTT p.(Leu556_Leu557insVal), 1.0 pt, PMID: 36983702) (PM3). At least one patient with this variant displayed progressive weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702). The highest population minor allele frequency is 0.0000008474 (1/1180036 alleles) in the European (non-Finnish) population in gnomAD v4.1.0, which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, 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; 02/25/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PVS1 ✔ The NM_003494.4: c.5181del p.(Glu1727AspfsTer7) variant in DYSF, which is also known as NM_001130987.2: c.5298del (p.Glu1766AspfsTer7), is a frameshift variant predicted to cause a premature stop codon in biologically

relevant exon 46/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PM3	✔	This variant has been reported in at least two individuals with clinical signs of limb girdle muscular dystrophy, including in a homozygous state (0.5 pts, PMID: 29970176) and confirmed in trans with a likely pathogenic or pathogenic variant (c.1668_1669insGTT p.(Leu556_Leu557insVal), 1.0 pt, PMID: 36983702) (PM3). Note that the homozygous individual was also homozygous for c.5626G>A p.(Asp1876Asn), which can be classified as Benign based on allele frequency (BA1). c.1668_1669insGTT can be classified as at least LP without this observation
PP4_Strong	✔	At least one patient with this variant displayed progressive weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 36983702). Rufibach et al. 2023 (PMID: 36983702) JF358: progressive proximal and distal weakness with initial calf hypertrophy that turned into atrophy, muscle biopsy showed dystrophic features, elevated CK. disease range dysferlin by blood monocyte assay. c.1668_1669insGTT p.(Leu556_Leu557insVal) in trans (P by VCEP)
PM2_Supporting	✔	The highest population minor allele frequency for this variant is 0.0000008474 (1/1180036 alleles) in the European (non-Finnish) population in gnomAD v4.1.0, which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.