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Variant: NM_001130987.2(DYSF):c.3859dup (p.Glu1287fs)

Version: 1.0

CA1706729

646166 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 186cfe64-f38b-4e2a-8246-cde26bdbfc5a
Approved on: 2025/4/11
Published on: 2025/5/16

HGVS expressions

NM_001130987.2(DYSF):c.3859dup (p.Glu1287fs)
NM_001130987.2:c.3859dup
NC_000002.12:g.71600804dup
CM000664.2:g.71600804dup
NC_000002.11:g.71827934dup
CM000664.1:g.71827934dup
NC_000002.10:g.71681442dup
NG_008694.1:g.152182dup
ENST00000698057.1:c.1231dup
ENST00000698058.1:c.448dup
ENST00000698059.1:c.448dup
ENST00000258104.8:c.3805dup
ENST00000410020.8:c.3859dup
ENST00000258104.7:c.3805dup
ENST00000394120.6:c.3808dup
ENST00000409366.5:c.3808dup
ENST00000409582.7:c.3856dup
ENST00000409651.5:c.3901dup
ENST00000409744.5:c.3766dup
ENST00000409762.5:c.3856dup
ENST00000410020.7:c.3859dup
ENST00000410041.1:c.3859dup
ENST00000413539.6:c.3898dup
ENST00000429174.6:c.3805dup
ENST00000475076.5:n.633dup
ENST00000479049.6:n.690dup
ENST00000493767.1:n.526dup
NM_001130455.1:c.3808dup
NM_001130976.1:c.3763dup
NM_001130977.1:c.3763dup
NM_001130978.1:c.3805dup
NM_001130979.1:c.3898dup
NM_001130980.1:c.3856dup
NM_001130981.1:c.3856dup
NM_001130982.1:c.3901dup
NM_001130983.1:c.3808dup
NM_001130984.1:c.3766dup

NM_001130985.1:c.3859dup
NM_001130986.1:c.3766dup
NM_001130987.1:c.3859dup
NM_003494.3:c.3805dup
NM_001130455.2:c.3808dup
NM_001130976.2:c.3763dup
NM_001130977.2:c.3763dup
NM_001130978.2:c.3805dup
NM_001130979.2:c.3898dup
NM_001130980.2:c.3856dup
NM_001130981.2:c.3856dup
NM_001130982.2:c.3901dup
NM_001130983.2:c.3808dup
NM_001130984.2:c.3766dup
NM_001130985.2:c.3859dup
NM_001130986.2:c.3766dup
NM_003494.4:c.3805dup

Pathogenic

Met criteria codes 4

PM3_Supporting PVS1
PM2_Supporting 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 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.3805dup p.(Glu1269GlyfsTer7) variant in DYSF, which is also known as NM_001130987.2: c.3859dup p.(Glu1287GlyfsTer7), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 34/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least two individuals with features of LGMD, including in unknown phase with a pathogenic variant (NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts, PMID: 27602406; 36983702; PM3_Supporting). At least one patient with this variant and a second presumed diagnostic variant in DYSF displayed a clinical suspicion of LGMD or progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 27602406; 36983702). The filtering allele frequency of this variant is 0.000020771 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 15/1112008 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 1.0.0; 04/11/2025): PVS1, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting	ℹ	✔	This variant has been detected in at least two individuals with features of LGMD, including in unknown phase with a pathogenic variant (c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts) (PMID: 27602406, 36983702; PM3_Supporting).
PVS1	ℹ	✔	The NM_003494.4: c.3805dup p.(Glu1269GlyfsTer7) variant in DYSF, which is also known as NM_001130987.2: c.3859dup p.(Glu1287GlyfsTer7), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 34/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting	ℹ	✔	The filtering allele frequency of this variant is 0.000020771 (the upper threshold of the 95% CI of 15/1112008 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PP4_Strong	ℹ	✔	At least one patient with this variant and a second presumed diagnostic variant in DYSF displayed a clinical suspicion of LGMD or progressive limb girdle muscle weakness and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 27602406, 36983702).

Curation History

Showing 1 to 1 of 1 rows

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