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Variant: NM_001130987.2(DYSF):c.128dup (p.Asn44fs)

Version: 1.0

CA916563969

2100759 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: ef97ff72-a898-45e8-a226-c1da2dd6652e
Approved on: 2025/2/25
Published on: 2025/3/7

HGVS expressions

NM_001130987.2:c.128dup
NM_001130987.2(DYSF):c.128dup (p.Asn44fs)
NC_000002.12:g.71480919dup
CM000664.2:g.71480919dup
NC_000002.11:g.71708049dup
CM000664.1:g.71708049dup
NC_000002.10:g.71561557dup
NG_008694.1:g.32297dup
ENST00000258104.8:c.125dup
ENST00000410020.8:c.128dup
ENST00000258104.7:c.125dup
ENST00000394120.6:c.128dup
ENST00000409366.5:c.128dup
ENST00000409582.7:c.125dup
ENST00000409651.5:c.128dup
ENST00000409744.5:c.128dup
ENST00000409762.5:c.125dup
ENST00000410020.7:c.128dup
ENST00000410041.1:c.128dup
ENST00000413539.6:c.125dup
ENST00000429174.6:c.125dup
NM_001130455.1:c.128dup
NM_001130976.1:c.125dup
NM_001130977.1:c.125dup
NM_001130978.1:c.125dup
NM_001130979.1:c.125dup
NM_001130980.1:c.125dup
NM_001130981.1:c.125dup
NM_001130982.1:c.128dup
NM_001130983.1:c.128dup
NM_001130984.1:c.128dup
NM_001130985.1:c.128dup
NM_001130986.1:c.128dup
NM_001130987.1:c.128dup
NM_003494.3:c.125dup
NM_001130455.2:c.128dup
NM_001130976.2:c.125dup

NM_001130977.2:c.125dup
NM_001130978.2:c.125dup
NM_001130979.2:c.125dup
NM_001130980.2:c.125dup
NM_001130981.2:c.125dup
NM_001130982.2:c.128dup
NM_001130983.2:c.128dup
NM_001130984.2:c.128dup
NM_001130985.2:c.128dup
NM_001130986.2:c.128dup
NM_003494.4:c.125dup

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PP4_Strong

Not Met criteria codes 2

PP1 PM3

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.125dup p.(Asn43GlufsTer6) variant in DYSF, which is also known as NM_001130987.2: c.128dup (p.Asn44GlufsTer6), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 2/55, 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 one individual with a diagnosis of Miyoshi myopathy, where it was identified in unknown phase with a second DYSF variant that can be classified as likely pathogenic independent of its observation in this patient (NM_003494.4: c.5159del p.(Arg1720LeufsTer2), 0.25 pts, PMID: 36983702; PM3_Supporting not met). This patient showed both progressive limb girdle muscle weakness and disease range dysferlin expression in blood monocytes (PMID: 36983702, Jain Foundation Registry internal data communication; PP4_Strong). The affected sibling of this patient carried the same two DYSF variants and also had disease range dysferlin protein expression in blood monocytes, but segregation could not be scored since the phase of the variants was not confirmed (PP1 not met). This variant is absent from gnomAD v2.1.1 and v4.1.0, although a different variant resulting in the same frameshift is present on one allele (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, PP4_Strong, PM2_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v4.1.0, although a different variant resulting in the same frameshift is present on one allele (PM2_Supporting).
PVS1	✔	The NM_003494.4: c.125dup p.(Asn43GlufsTer6) variant in DYSF, which is also known as NM_001130987.2: c.128dup (p.Asn44GlufsTer6), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon

2/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PP4_Strong	✔	At least one individual with this variant experienced progressive limb girdle muscle weakness and showed disease range dysferlin expression in blood monocytes (PMID: 36983702, Jain Foundation Registry internal data communication; PP4_Strong).

Not Met criteria codes

PP1	✖	The affected sibling of one patient carried the same two DYSF variants and also had disease range dysferlin protein expression in blood monocytes, but the phase of the variants was not confirmed (PMID: 36983702, Jain Foundation Dysferlin Registry internal data communication; PP1 not met).
PM3	✖	This variant has been reported in one individual with a clinical or genetic suspicion of dysferlinopathy, where it was identified in unknown phase with a second DYSF variant that can be classified as likely pathogenic independent of its observation in this patient (c.5159del p.(Arg1720LeufsTer2), 0.25 pts, PMID: 36983702; PM3_Supporting not met).

Curation History

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