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Variant: NM_001130987.2(DYSF):c.1488dup (p.Asp497fs)

Version: 1.0

CA222127

94271 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d860540d-b737-48aa-8f08-93542db1421b
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2(DYSF):c.1488dup (p.Asp497fs)
NM_001130987.2:c.1488dup
NC_000002.12:g.71535306dup
CM000664.2:g.71535306dup
NC_000002.11:g.71762436dup
CM000664.1:g.71762436dup
NC_000002.10:g.71615944dup
NG_008694.1:g.86684dup
ENST00000258104.8:c.1392dup
ENST00000410020.8:c.1488dup
ENST00000258104.7:c.1392dup
ENST00000394120.6:c.1395dup
ENST00000409366.5:c.1395dup
ENST00000409582.7:c.1485dup
ENST00000409651.5:c.1488dup
ENST00000409744.5:c.1395dup
ENST00000409762.5:c.1485dup
ENST00000410020.7:c.1488dup
ENST00000410041.1:c.1488dup
ENST00000413539.6:c.1485dup
ENST00000429174.6:c.1392dup
NM_001130455.1:c.1395dup
NM_001130976.1:c.1392dup
NM_001130977.1:c.1392dup
NM_001130978.1:c.1392dup
NM_001130979.1:c.1485dup
NM_001130980.1:c.1485dup
NM_001130981.1:c.1485dup
NM_001130982.1:c.1488dup
NM_001130983.1:c.1395dup
NM_001130984.1:c.1395dup
NM_001130985.1:c.1488dup
NM_001130986.1:c.1395dup
NM_001130987.1:c.1488dup
NM_003494.3:c.1392dup
NM_001130455.2:c.1395dup
NM_001130976.2:c.1392dup

NM_001130977.2:c.1392dup
NM_001130978.2:c.1392dup
NM_001130979.2:c.1485dup
NM_001130980.2:c.1485dup
NM_001130981.2:c.1485dup
NM_001130982.2:c.1488dup
NM_001130983.2:c.1395dup
NM_001130984.2:c.1395dup
NM_001130985.2:c.1488dup
NM_001130986.2:c.1395dup
NM_003494.4:c.1392dup

Pathogenic

Met criteria codes 4

PM3 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.1392dup p.(Asp465ArgfsTer9) variant in DYSF, which is also known as NM_001130987.2: c.1488dup (p.Asp497ArgfsTer9), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 16/55, 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 five individuals with features of LGMD (PMID: 27602406, 36983702), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 27602406) and in unknown phase with a pathogenic variant in two patients (NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts, PMID: 27602406; NM_003494.4: c.1481-1G>A, 0.5 pts, PMID: 27602406) (PM3). At least one patient with this variant displayed a clinical suspicion of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 27602406, 33610434). The filtering allele frequency of this variant is 0.000012981 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 8/1111992 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; 07/29/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3	✔	This variant has been detected in at least five individuals with features of LGMD (PMID: 27602406, 36983702), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 27602406) and in unknown phase with a pathogenic variant in two patients (NM_003494.4: c.5698_5699del p.(Ser1900GlnfsTer14), 0.5 pts, PMID: 27602406; NM_003494.4: c.1481-1G>A, 0.5 pts, PMID: 27602406) (PM3). c.5698_5699del p.(Ser1900GlnfsTer14) and c.1481-1G>A are independently P the curated variant and

c.5698_5699del p.(Ser1900GlnfsTer14) are predicted on different haplotypes c.1481-1G>A is absent from gnomAD v2

PVS1	✔	The NM_003494.4: c.1392dup p.(Asp465ArgfsTer9) variant in DYSF, which is also known as NM_001130987.2: c.1488dup (p.Asp497ArgfsTer9), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 16/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The filtering allele frequency of this variant is 0.000012981 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 8/1111992 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PP4_Strong	✔	At least one patient with this variant displayed a clinical suspicion of LGMD and severely reduced or absent dysferlin protein expression in skeletal muscle or blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 27602406, 33610434).

Curation History

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