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.959dup (p.Asp320fs)

Version: 1.0

CA533254006

2674961 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: b74affdc-5f90-46bf-b094-50f735774930
Approved on: 2025/7/29
Published on: 2025/8/14

HGVS expressions

NM_001130987.2(DYSF):c.959dup (p.Asp320fs)
NM_001130987.2:c.959dup
NC_000002.12:g.71516996dup
CM000664.2:g.71516996dup
NC_000002.11:g.71744126dup
CM000664.1:g.71744126dup
NC_000002.10:g.71597634dup
NG_008694.1:g.68374dup
ENST00000258104.8:c.863dup
ENST00000410020.8:c.959dup
ENST00000258104.7:c.863dup
ENST00000394120.6:c.866dup
ENST00000409366.5:c.866dup
ENST00000409582.7:c.956dup
ENST00000409651.5:c.959dup
ENST00000409744.5:c.866dup
ENST00000409762.5:c.956dup
ENST00000410020.7:c.959dup
ENST00000410041.1:c.959dup
ENST00000413539.6:c.956dup
ENST00000429174.6:c.863dup
NM_001130455.1:c.866dup
NM_001130976.1:c.863dup
NM_001130977.1:c.863dup
NM_001130978.1:c.863dup
NM_001130979.1:c.956dup
NM_001130980.1:c.956dup
NM_001130981.1:c.956dup
NM_001130982.1:c.959dup
NM_001130983.1:c.866dup
NM_001130984.1:c.866dup
NM_001130985.1:c.959dup
NM_001130986.1:c.866dup
NM_001130987.1:c.959dup
NM_003494.3:c.863dup
NM_001130455.2:c.866dup
NM_001130976.2:c.863dup

NM_001130977.2:c.863dup
NM_001130978.2:c.863dup
NM_001130979.2:c.956dup
NM_001130980.2:c.956dup
NM_001130981.2:c.956dup
NM_001130982.2:c.959dup
NM_001130983.2:c.866dup
NM_001130984.2:c.866dup
NM_001130985.2:c.959dup
NM_001130986.2:c.866dup
NM_003494.4:c.863dup

Pathogenic

Met criteria codes 3

PM3_Supporting PVS1 PM2_Supporting

Not Met criteria codes 1

PP4

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.863dup p.(Asp288GlufsTer40) variant in DYSF, which is also known as NM_001130987.2: c.959dup p.(Asp320GlufsTer40), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 11/55, 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 two individuals with dysferlinopathy (PMID: 36983702, 33715265, 14673575; LOVD DYSF_000186), including in unknown phase with a pathogenic variant (NM_003494.4: c.3031+2T>C, 0.5 pts, PMID: 36983702; PM3_Supporting). The filtering allele frequency of this variant in gnomAD v4.1.0 exomes is 0.000008232 (the upper threshold of the 95% CI of 4/1111996 European (non-Finnish) chromosomes), which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets 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; 07/29/2025): PVS1, PM3_Supporting, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been identified in at least two individuals with dysferlinopathy (PMID: 36983702, 33715265, 14673575; LOVD DYSF_000186), including in unknown phase with a pathogenic variant (NM_003494.4: c.3031+2T>C, 0.5 pts, PMID: 36983702; PM3_Supporting). c.3031+2T>C is independently classified as P and is not found in gnomAD v2 so cannot check co-occurrence
PVS1	✔	The NM_003494.4: c.863dup p.(Asp288GlufsTer40) variant in DYSF, which is also known as NM_001130987.2: c.959dup p.(Asp320GlufsTer40), is a frameshift variant predicted to cause a premature stop codon in biologically

relevant exon 11/55, 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 in gnomADv4.1.0 exomes is 0.000008232 (the upper threshold of the 95% CI of 4/1111996 European (non-Finnish) chromosomes), which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

PP4 ✖

Cannot conclusively determine that one patient met genetic, clinical, and protein expression criteria. Cannot definitively confirm that Fernández-Eulate and Rufibach cases are the same individual, and cannot exclude possibility that in Fernández-Eulate case, protein expression was from family member. Walter case had only 1 presumed diagnostic variant identified.

Curation History

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