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.951+1del

Version: 1.0

CA253921

6684 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 893c0a55-bb7e-44b1-98d2-d451b50068dc
Approved on: 2025/1/8
Published on: 2025/1/8

HGVS expressions

NM_001130987.2(DYSF):c.951+1del
NM_001130987.2:c.951+1del
NC_000002.12:g.71516243del
CM000664.2:g.71516243del
NC_000002.11:g.71743373del
CM000664.1:g.71743373del
NC_000002.10:g.71596881del
NG_008694.1:g.67621del
ENST00000258104.8:c.855+1del
ENST00000410020.8:c.951+1del
ENST00000258104.7:c.855+1del
ENST00000394120.6:c.858+1del
ENST00000409366.5:c.858+1del
ENST00000409582.7:c.948+1del
ENST00000409651.5:c.951+1del
ENST00000409744.5:c.858+1del
ENST00000409762.5:c.948+1del
ENST00000410020.7:c.951+1del
ENST00000410041.1:c.951+1del
ENST00000413539.6:c.948+1del
ENST00000429174.6:c.855+1del
NM_001130455.1:c.858+1del
NM_001130976.1:c.855+1del
NM_001130977.1:c.855+1del
NM_001130978.1:c.855+1del
NM_001130979.1:c.948+1del
NM_001130980.1:c.948+1del
NM_001130981.1:c.948+1del
NM_001130982.1:c.951+1del
NM_001130983.1:c.858+1del
NM_001130984.1:c.858+1del
NM_001130985.1:c.951+1del
NM_001130986.1:c.858+1del
NM_001130987.1:c.951+1del
NM_003494.3:c.855+1del
NM_001130455.2:c.858+1del
NM_001130976.2:c.855+1del

NM_001130977.2:c.855+1del
NM_001130978.2:c.855+1del
NM_001130979.2:c.948+1del
NM_001130980.2:c.948+1del
NM_001130981.2:c.948+1del
NM_001130982.2:c.951+1del
NM_001130983.2:c.858+1del
NM_001130984.2:c.858+1del
NM_001130985.2:c.951+1del
NM_001130986.2:c.858+1del
NM_003494.4:c.855+1del

Pathogenic

Met criteria codes 4

PM3_Strong PP4_Strong PVS1 PP1

Not Met criteria codes 1

PM2

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.855+1del variant in DYSF, which is also known as NM_001130987.2: c.951+1del, occurs within the canonical splice donor site of intron 8. It is predicted to cause skipping of biologically relevant exon 8/55, resulting in an in-frame deletion of 21 amino acids (PVS1_Moderate). RNAseq data has confirmed that this variant results in in aberrant splicing, suggesting use of an alternative acceptor site that deletes the first basepair of DYSF exon 9 and leads to a frameshift and premature truncation p.(Val286TrpfsTer2) (PMID: 36983702). This variant has been detected in at least 12 individuals with limb girdle muscular dystrophy (PMID: 20544924, 17828519, 18853459, 36983702). Of those individuals, at least two were compound heterozygous for the variant and a pathogenic variant (c.3504dup p.(Lys1169GlnfsTer6), 1.0 pt, PMID: 20544924; c.3126G>A p.(Trp1024Ter): 1.0 pt, PMID: 18853459), and at least one was homozygous (0.25 pts, PMID: 18853459) (PM3_Strong). At least one patient with this variant displayed progressive limb-girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 18853459, 36983702). The variant was also reported to co-segregate with the disease in two affected family members from two families (PMID: 18853459) (PP1, capped with PP4_Strong). The filtering allele frequency of the variant is 0.0009441 for Admixed American genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 8/15286), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). 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; 01/08/2025): PVS1_Moderate, PM3_Strong, PP4_Strong, PP1.

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least 12 individuals with limb girdle muscular dystrophy (PMID: 20544924, 17828519, 18853459, 36983702). Of those individuals, at least two were compound heterozygous for the variant

and a pathogenic variant (c.3504dup p.(Lys1169GlnfsTer6), 1.0 pt, PMID: 20544924; c.3126G>A p.(Trp1024Ter): 1.0 pt, PMID: 18853459), and at least one was homozygous (0.25 pts, PMID: 18853459) (PM3_Strong).

PP4_Strong	✔	At least one patient with this variant displayed progressive limb-girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 18853459, 36983702).
PVS1	✔	The NM_003494.4: c.855+1del variant in DYSF, which is also known as NM_001130987.2: c.951+1del, occurs within the canonical splice donor site (+/- 1,2) of intron 8. RNAseq data has confirmed that this variant results in aberrant splicing, suggesting use of an alternative acceptor site that deletes the first basepair of DYSF exon 9 and leads to a frameshift and premature truncation p.(Val286TrpfsTer2) (PMID: 36983702) (PVS1_RNA).
PP1	✔	The variant was reported to co-segregate with the disease in two affected family members from two families (PMID: 18853459) (PP1). (capped with PP4_strong)

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variants is 0.0009441 for Admixed American genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 8/15286), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

Showing 1 to 1 of 1 rows

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