Variant: NM_001130987.2(DYSF):c.2760dup (p.Lys921fs)

Version: 1.0

CA913189537

592961 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 57147eaf-45a9-4391-975f-5c32bb0849bd
Approved on: 2025-03-19
Published on: 2025-04-04

HGVS expressions

NM_001130987.2:c.2760dup
NM_001130987.2(DYSF):c.2760dup (p.Lys921fs)
NC_000002.12:g.71568234dup
CM000664.2:g.71568234dup
NC_000002.11:g.71795364dup
CM000664.1:g.71795364dup
NC_000002.10:g.71648872dup
NG_008694.1:g.119612dup
ENST00000698057.1:c.132dup
ENST00000258104.8:c.2706dup
ENST00000410020.8:c.2760dup
ENST00000258104.7:c.2706dup
ENST00000394120.6:c.2709dup
ENST00000409366.5:c.2709dup
ENST00000409582.7:c.2757dup
ENST00000409651.5:c.2802dup
ENST00000409744.5:c.2667dup
ENST00000409762.5:c.2757dup
ENST00000410020.7:c.2760dup
ENST00000410041.1:c.2760dup
ENST00000413539.6:c.2799dup
ENST00000429174.6:c.2706dup
NM_001130455.1:c.2709dup
NM_001130976.1:c.2664dup
NM_001130977.1:c.2664dup
NM_001130978.1:c.2706dup
NM_001130979.1:c.2799dup
NM_001130980.1:c.2757dup
NM_001130981.1:c.2757dup
NM_001130982.1:c.2802dup
NM_001130983.1:c.2709dup
NM_001130984.1:c.2667dup
NM_001130985.1:c.2760dup
NM_001130986.1:c.2667dup
NM_001130987.1:c.2760dup
NM_003494.3:c.2706dup
NM_001130455.2:c.2709dup

NM_001130976.2:c.2664dup
NM_001130977.2:c.2664dup
NM_001130978.2:c.2706dup
NM_001130979.2:c.2799dup
NM_001130980.2:c.2757dup
NM_001130981.2:c.2757dup
NM_001130982.2:c.2802dup
NM_001130983.2:c.2709dup
NM_001130984.2:c.2667dup
NM_001130985.2:c.2760dup
NM_001130986.2:c.2667dup
NM_003494.4:c.2706dup

Pathogenic

Met criteria codes 4

PP4_Strong | PM2_Supporting | PM3 | PVS1

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.2706dup p.(Lys903GlnfsTer4) variant in DYSF, which is also known as NM_001130987.2: c.2760dup p.(Lys921GlnfsTer4), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 26/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been observed in at least eight individuals with features consistent with LGMD (PMID: 21522182, 22616201; Jain Foundation Dysferlin Registry internal data communication), including in a homozygous state in one patient without familial consanguinity (0.5 pts) and one Iranian individual with known familial consanguinity (0.25 pts) (Jain Foundation Dysferlin Registry internal data communication). In another patient, it was observed in trans with a likely pathogenic or pathogenic DYSF variant (NM_003494.4: c.4024C>T p.(Arg1342Trp), 1.0 pt, PMID: 21522182, 22616201) (PM3). At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness as well as absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 22616201, 21522182; PP4_Strong). This variant is absent from gnomAD v4.1.0 (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; 03/19/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness as well as absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 22616201, 21522182; PP4_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

PM3	✔	This variant has been observed in at least eight individuals with features consistent with LGMD (PMID: 21522182, 22616201; Jain Foundation Dysferlin Registry internal data communication), including in a homozygous state in one patient without familial consanguinity (0.5 pts) and one Iranian individual with known consanguinity (0.25 pts) (Jain Foundation Dysferlin Registry internal data communication). In another patient, it was observed in trans with a likely pathogenic or pathogenic DYSF variant (NM_003494.4: c.4024C>T p.(Arg1342Trp), 1.0 pt, PMID: 21522182, 22616201) (PM3). c.4024C>T p.(Arg1342Trp) can be classified as LP independent of their co-occurrence in this individual
PVS1	✔	The NM_003494.4: c.2706dup p.(Lys903GlnfsTer4) variant in DYSF, which is also known as NM_001130987.2: c.2760dup p.(Lys921GlnfsTer4), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 26/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001130987.2(DYSF):c.2760dup (p....	Pathogenic	Autosomal Recessive Limb-Girdle Muscular Dystrophy	2025-04-04	1.0	ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for DYSF Version 1.0.0	DYSF

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