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Variant: NM_001130987.2(DYSF):c.3571dup (p.Ser1191fs)

Version: 1.0

CA1706625

370730 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: a79f18ca-d9c8-4b52-8b8a-60cafde5a05f
Approved on: 2025/5/14
Published on: 2025/6/6

HGVS expressions

NM_001130987.2(DYSF):c.3571dup (p.Ser1191fs)
NM_001130987.2:c.3571dup
NC_000002.12:g.71590285dup
CM000664.2:g.71590285dup
NC_000002.11:g.71817415dup
CM000664.1:g.71817415dup
NC_000002.10:g.71670923dup
NG_008694.1:g.141663dup
ENST00000698057.1:c.943dup
ENST00000698058.1:c.160dup
ENST00000698059.1:c.160dup
ENST00000258104.8:c.3517dup
ENST00000410020.8:c.3571dup
ENST00000258104.7:c.3517dup
ENST00000394120.6:c.3520dup
ENST00000409366.5:c.3520dup
ENST00000409582.7:c.3568dup
ENST00000409651.5:c.3613dup
ENST00000409744.5:c.3478dup
ENST00000409762.5:c.3568dup
ENST00000410020.7:c.3571dup
ENST00000410041.1:c.3571dup
ENST00000413539.6:c.3610dup
ENST00000429174.6:c.3517dup
ENST00000475076.5:n.345dup
ENST00000479049.6:n.402dup
ENST00000493767.1:n.238dup
NM_001130455.1:c.3520dup
NM_001130976.1:c.3475dup
NM_001130977.1:c.3475dup
NM_001130978.1:c.3517dup
NM_001130979.1:c.3610dup
NM_001130980.1:c.3568dup
NM_001130981.1:c.3568dup
NM_001130982.1:c.3613dup
NM_001130983.1:c.3520dup
NM_001130984.1:c.3478dup

NM_001130985.1:c.3571dup
NM_001130986.1:c.3478dup
NM_001130987.1:c.3571dup
NM_003494.3:c.3517dup
NM_001130455.2:c.3520dup
NM_001130976.2:c.3475dup
NM_001130977.2:c.3475dup
NM_001130978.2:c.3517dup
NM_001130979.2:c.3610dup
NM_001130980.2:c.3568dup
NM_001130981.2:c.3568dup
NM_001130982.2:c.3613dup
NM_001130983.2:c.3520dup
NM_001130984.2:c.3478dup
NM_001130985.2:c.3571dup
NM_001130986.2:c.3478dup
NM_003494.4:c.3517dup

Pathogenic

Met criteria codes 4

PP4_Strong PM3_Strong PVS1 PM2_Supporting

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.3517dup p.(Ser1173PhefsTer2) variant in DYSF, which is also known as NM_001130987.2: c.3571dup p.(Ser1191PhefsTer2), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 32/55, 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 at least six patients with dysferlinopathy (PMID: 19528035, 18853459, 27447704, 36983702), including in a homozygous state in two individuals without reported familial consanguinity (1.0 pts, PMID: 19528035, 27447704), confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.3113G>A p.(Arg1038Gln), 1.0 pt, PMID: 36983702), and in unknown phase with a pathogenic variant (NM_003494.4: c.5836_5839del p.(Gln1946TrpfsTer19), 0.5 pts, PMID: 36983702) (PM3_Strong). At least one of the patients with this variant and a second presumed diagnostic DYSF variant displayed progressive proximal muscle weakness and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 18853459, 36983702). The filtering allele frequency of this variant is 0.000053899 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 47/1111990 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; 05/14/2025): PVS1, PM3_Strong, PP4_Strong, PM2_Supporting.

Met criteria codes

PP4_Strong	✔	At least one of the patients with this variant and a second presumed diagnostic DYSF variant displayed progressive proximal muscle weakness and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 18853459, 36983702).
PM3_Strong	✔	This variant has been reported in at least six patients with dysferlinopathy (PMID: 19528035, 18853459, 27447704, 36983702), including in a homozygous state in two individuals without reported familial consanguinity (1.0 pts, PMID: 19528035, 27447704), confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.3113G>A p.(Arg1038Gln), 1.0 pt, PMID: 36983702), and in unknown phase with a pathogenic variant (NM_003494.4: c.5836_5839del p.(Gln1946TrpfsTer19), 0.5 pts, PMID: 36983702) (PM3_Strong). Not possible to check co-occurrence
PVS1	✔	The NM_003494.4: c.3517dup p.(Ser1173PhefsTer2) variant in DYSF, which is also known as NM_001130987.2: c.3571dup (p.Ser1191PhefsTer2), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 32/55, 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 0.000053899 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 47/1111990 European (non-Finnish) chromosomes) , which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Curation History

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