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Variant: NM_001130987.2(DYSF):c.895_896del (p.Phe299fs)

Version: 1.0

CA533253809

639814 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: f05d0b1b-36b6-454e-a404-5ce25ea211ad
Approved on: 2025/5/28
Published on: 2025/6/6

HGVS expressions

NM_001130987.2:c.895_896del
NM_001130987.2(DYSF):c.895_896del (p.Phe299fs)
NC_000002.12:g.71516186_71516187del
CM000664.2:g.71516186_71516187del
NC_000002.11:g.71743316_71743317del
CM000664.1:g.71743316_71743317del
NC_000002.10:g.71596824_71596825del
NG_008694.1:g.67564_67565del
ENST00000258104.8:c.799_800del
ENST00000410020.8:c.895_896del
ENST00000258104.7:c.799_800del
ENST00000394120.6:c.802_803del
ENST00000409366.5:c.802_803del
ENST00000409582.7:c.892_893del
ENST00000409651.5:c.895_896del
ENST00000409744.5:c.802_803del
ENST00000409762.5:c.892_893del
ENST00000410020.7:c.895_896del
ENST00000410041.1:c.895_896del
ENST00000413539.6:c.892_893del
ENST00000429174.6:c.799_800del
NM_001130455.1:c.802_803del
NM_001130976.1:c.799_800del
NM_001130977.1:c.799_800del
NM_001130978.1:c.799_800del
NM_001130979.1:c.892_893del
NM_001130980.1:c.892_893del
NM_001130981.1:c.892_893del
NM_001130982.1:c.895_896del
NM_001130983.1:c.802_803del
NM_001130984.1:c.802_803del
NM_001130985.1:c.895_896del
NM_001130986.1:c.802_803del
NM_001130987.1:c.895_896del
NM_003494.3:c.799_800del
NM_001130455.2:c.802_803del
NM_001130976.2:c.799_800del

NM_001130977.2:c.799_800del
NM_001130978.2:c.799_800del
NM_001130979.2:c.892_893del
NM_001130980.2:c.892_893del
NM_001130981.2:c.892_893del
NM_001130982.2:c.895_896del
NM_001130983.2:c.802_803del
NM_001130984.2:c.802_803del
NM_001130985.2:c.895_896del
NM_001130986.2:c.802_803del
NM_003494.4:c.799_800del

Pathogenic

Met criteria codes 4

PM3_Supporting 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.799_800del p.(Phe267LeufsTer5) variant in DYSF, which is also known as NM_001130987.2: c.895_896del p.(Phe299LeufsTer5), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 8/55, 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 seven patients with suspected LGMD or dysferlinopathy (PMID: 18853459, 25591676, 27647186, 30107846), including in a homozygous state in at least one individual with no known familial consanguinity (0.5 pts, PMID: 27647186; PM3_Supporting). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 18853459; PP4_Strong). The highest minor allele frequency for this variant is 0.00002519 in the East Asian population in gnomAD v4.1.0 (1/39700 exome 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; 05/28/2025): PVS1, PM3_Supporting, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3_Supporting ✔

This variant has been reported in at least seven patients with suspected LGMD or dysferlinopathy (PMID: 18853459, 25591676, 27647186, 30107846), including in a homozygous state in at least one individual with no known familial consanguinity (0.5 pts, PMID: 27647186; PM3_supporting). Five individuals have a second variant that has not yet been curated by the LGMD VCEP. In addition, one homozygous individual has another heterozygous variant. Therefore, only one homozygous individual has been included for PM3 evidence in the summary.

PVS1		✔	The NM_003494.4: c.799_800del p.(Phe267LeufsTer5) variant in DYSF, which is also known as NM_001130987.2: c.895_896del p.(Phe299LeufsTer5), is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 8/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting		✔	The highest minor allele frequency for this variant is 0.00002519 in the East Asian population in gnomAD v4.1.0 (1/39700 exome chromosomes), which is lower than the ClinGen LGMD VCEP threshold (0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).
PP4_Strong		✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-related LGMD (PMID: 18853459; PP4_Strong).

Curation History

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