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Variant: NM_001130987.2(DYSF):c.3886C>T (p.Gln1296Ter)

Version: 1.0

CA233937

167025 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: ade59672-587e-472c-89db-6042fc458dc7
Approved on: 2025/3/6
Published on: 2025/4/4

HGVS expressions

NM_001130987.2(DYSF):c.3886C>T (p.Gln1296Ter)
NM_001130987.2:c.3886C>T
NC_000002.12:g.71600831C>T
CM000664.2:g.71600831C>T
NC_000002.11:g.71827961C>T
CM000664.1:g.71827961C>T
NC_000002.10:g.71681469C>T
NG_008694.1:g.152209C>T
ENST00000698057.1:c.1258C>T
ENST00000698058.1:c.475C>T
ENST00000698059.1:c.475C>T
ENST00000258104.8:c.3832C>T
ENST00000410020.8:c.3886C>T
ENST00000258104.7:c.3832C>T
ENST00000394120.6:c.3835C>T
ENST00000409366.5:c.3835C>T
ENST00000409582.7:c.3883C>T
ENST00000409651.5:c.3928C>T
ENST00000409744.5:c.3793C>T
ENST00000409762.5:c.3883C>T
ENST00000410020.7:c.3886C>T
ENST00000410041.1:c.3886C>T
ENST00000413539.6:c.3925C>T
ENST00000429174.6:c.3832C>T
ENST00000475076.5:n.660C>T
ENST00000479049.6:n.717C>T
ENST00000493767.1:n.553C>T
NM_001130455.1:c.3835C>T
NM_001130976.1:c.3790C>T
NM_001130977.1:c.3790C>T
NM_001130978.1:c.3832C>T
NM_001130979.1:c.3925C>T
NM_001130980.1:c.3883C>T
NM_001130981.1:c.3883C>T
NM_001130982.1:c.3928C>T
NM_001130983.1:c.3835C>T
NM_001130984.1:c.3793C>T

NM_001130985.1:c.3886C>T
NM_001130986.1:c.3793C>T
NM_001130987.1:c.3886C>T
NM_003494.3:c.3832C>T
NM_001130455.2:c.3835C>T
NM_001130976.2:c.3790C>T
NM_001130977.2:c.3790C>T
NM_001130978.2:c.3832C>T
NM_001130979.2:c.3925C>T
NM_001130980.2:c.3883C>T
NM_001130981.2:c.3883C>T
NM_001130982.2:c.3928C>T
NM_001130983.2:c.3835C>T
NM_001130984.2:c.3793C>T
NM_001130985.2:c.3886C>T
NM_001130986.2:c.3793C>T
NM_003494.4:c.3832C>T

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM3_Strong 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.3832C>T p.(Gln1278Ter) variant in DYSF, which is also known as NM_001130987.2: c.3886C>T p.(Gln1296Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 34/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least five individuals with features of LGMD (PMID: 27602406, 36983702, 16010686, 17698709, 18853459), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 16010686) and confirmed in trans with a pathogenic variant (NM_003494.4: c.1663C>T p.(Arg555Trp), 1.0 pt, PMID: 16010686). It was also identified in unknown phase with a pathogenic variant (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 27602406) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16010686, 18853459). The filtering allele frequency (the upper threshold of the 95% CI of 48/1111982 exome chromosomes) is 0.000054905 for the European (non-Finnish) population in gnomAD v4.1.0, 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; 03/06/2025): PVS1, PM3_Strong, PP4_Strong, PM2_Supporting.

Met criteria codes

PVS1	✔	The NM_003494.4: c.3832C>T p.(Gln1278Ter) variant in DYSF, which is also known as NM_001130987.2: c.3886C>T p.(Gln1296Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 34/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16010686, 18853459).
PM3_Strong	✔	This variant has been detected in at least five individuals with features of LGMD (PMID: 27602406, 36983702, 16010686, 17698709, 18853459), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 16010686) and confirmed in trans with a pathogenic variant (NM_003494.4: c.1663C>T p.(Arg555Trp), 1.0 pt, PMID: 16010686). It was also identified in unknown phase with a pathogenic variant (NM_003494.4: c.857T>A p.(Val286Glu), 0.5 pts, PMID: 27602406) (PM3_Strong).
PM2_Supporting	✔	The filtering allele frequency (the upper threshold of the 95% CI of 48/1111982 exome chromosomes) is 0.000054905 for the European (non-Finnish) population in gnomAD v4.1.0, which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting and therefore meets this criterion (PM2_Supporting).

Curation History

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