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Variant: NM_001130987.2(DYSF):c.4873C>T (p.Arg1625Ter)

Version: 1.0

CA222174

94330 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7c197707-5386-4dad-acb3-5912cd701658
Approved on: 2025/4/16
Published on: 2025/5/16

HGVS expressions

NM_001130987.2(DYSF):c.4873C>T (p.Arg1625Ter)
NM_001130987.2:c.4873C>T
NC_000002.12:g.71658995C>T
CM000664.2:g.71658995C>T
NC_000002.11:g.71886125C>T
CM000664.1:g.71886125C>T
NC_000002.10:g.71739633C>T
NG_008694.1:g.210373C>T
ENST00000698057.1:c.2287C>T
ENST00000698058.1:c.1504C>T
ENST00000698059.1:c.1612C>T
ENST00000258104.8:c.4756C>T
ENST00000410020.8:c.4873C>T
ENST00000258104.7:c.4756C>T
ENST00000394120.6:c.4759C>T
ENST00000409366.5:c.4822C>T
ENST00000409582.7:c.4870C>T
ENST00000409651.5:c.4852C>T
ENST00000409744.5:c.4780C>T
ENST00000409762.5:c.4807C>T
ENST00000410020.7:c.4873C>T
ENST00000410041.1:c.4810C>T
ENST00000413539.6:c.4849C>T
ENST00000429174.6:c.4819C>T
ENST00000479049.6:n.1641C>T
NM_001130455.1:c.4759C>T
NM_001130976.1:c.4714C>T
NM_001130977.1:c.4777C>T
NM_001130978.1:c.4819C>T
NM_001130979.1:c.4849C>T
NM_001130980.1:c.4807C>T
NM_001130981.1:c.4870C>T
NM_001130982.1:c.4852C>T
NM_001130983.1:c.4822C>T
NM_001130984.1:c.4780C>T
NM_001130985.1:c.4810C>T
NM_001130986.1:c.4717C>T

NM_001130987.1:c.4873C>T
NM_003494.3:c.4756C>T
NM_001130455.2:c.4759C>T
NM_001130976.2:c.4714C>T
NM_001130977.2:c.4777C>T
NM_001130978.2:c.4819C>T
NM_001130979.2:c.4849C>T
NM_001130980.2:c.4807C>T
NM_001130981.2:c.4870C>T
NM_001130982.2:c.4852C>T
NM_001130983.2:c.4822C>T
NM_001130984.2:c.4780C>T
NM_001130985.2:c.4810C>T
NM_001130986.2:c.4717C>T
NM_003494.4:c.4756C>T

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PM3_Strong

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.4756C>T p.(Arg1586Ter) variant in DYSF, which is also known as NM_001130987.2: c.4873C>T p.(Arg1625Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 43/55, 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 five patients with features consistent with LGMD (PMID: 36983702; 23641709; 23530687; 11468312), including in a homozygous state in one individual without reported familial consanguinity (0.5 pts, PMID: 11468312) and in trans with a likely pathogenic or pathogenic variant in two individuals (NM_003494.4: c.265C>T p.(Arg89Ter), 1.0 pt, PMID: 23641709; NM_003494.4: c.3113G>C p.(Arg1038Pro), 1.0 pt, PMID: 36983702) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic variant in DYSF had a clinical diagnosis of LGMD (Miyoshi myopathy) and absent dysferlin protein expression in both skeletal muscle and blood monocytes, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 36983702; 33610434). The filtering allele frequency of this variant is 0.0001061 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 4/86258 South Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting 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; 04/16/2025): PVS1, PM3_Strong, PP4_Strong.

Met criteria codes

PVS1 ✔

The NM_003494.4: c.4756C>T p.(Arg1586Ter) variant in DYSF, which is also known as NM_001130987.2: c.4873C>T p.(Arg1625Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 43/55, 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 variant in DYSF had a clinical diagnosis of LGMD (Miyoshi myopathy) and absent dysferlin protein expression in both skeletal muscle and blood monocytes, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID: 36983702, 33610434).
PM3_Strong	✔	This variant has been reported in at least five patients with features consistent with LGMD (PMID: 36983702, 23641709, 23530687, 11468312), including in a homozygous state in one individual without reported familial consanguinity (0.5 pts, PMID: 11468312) and in trans with a likely pathogenic or pathogenic variant in two individuals (c.265C>T p.(Arg89Ter), 1.0 pt, PMID: 23641709; c.3113G>C p.(Arg1038Pro), 1.0 pt, PMID: 36983702) (PM3_Strong). c.265C>T p.(Arg89Ter) can be classified as at least LP independently (PVS1, PM2_Supporting) c.3113G>C p.(Arg1038Pro) can be classified as at least LP independently (PM2_Supporting, PS3_Moderate, PP3, PM5)

Not Met criteria codes

PM2	✖	The filtering allele frequency of this variant is 0.0001061 (the upper threshold of the 95% CI of 4/86258 South Asian exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met).

Curation History

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