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Variant: NM_001130987.2(DYSF):c.268C>T (p.Arg90Ter)

Version: 1.0

CA275254

197217 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8012ad07-ac5b-4609-a73d-0855852174e7
Approved on: 2025/4/16
Published on: 2025/5/16

HGVS expressions

NM_001130987.2:c.268C>T
NM_001130987.2(DYSF):c.268C>T (p.Arg90Ter)
NC_000002.12:g.71503242C>T
CM000664.2:g.71503242C>T
NC_000002.11:g.71730372C>T
CM000664.1:g.71730372C>T
NC_000002.10:g.71583880C>T
NG_008694.1:g.54620C>T
ENST00000258104.8:c.265C>T
ENST00000410020.8:c.268C>T
ENST00000258104.7:c.265C>T
ENST00000394120.6:c.268C>T
ENST00000409366.5:c.268C>T
ENST00000409582.7:c.265C>T
ENST00000409651.5:c.268C>T
ENST00000409744.5:c.268C>T
ENST00000409762.5:c.265C>T
ENST00000410020.7:c.268C>T
ENST00000410041.1:c.268C>T
ENST00000413539.6:c.265C>T
ENST00000429174.6:c.265C>T
NM_001130455.1:c.268C>T
NM_001130976.1:c.265C>T
NM_001130977.1:c.265C>T
NM_001130978.1:c.265C>T
NM_001130979.1:c.265C>T
NM_001130980.1:c.265C>T
NM_001130981.1:c.265C>T
NM_001130982.1:c.268C>T
NM_001130983.1:c.268C>T
NM_001130984.1:c.268C>T
NM_001130985.1:c.268C>T
NM_001130986.1:c.268C>T
NM_001130987.1:c.268C>T
NM_003494.3:c.265C>T
NM_001130455.2:c.268C>T
NM_001130976.2:c.265C>T

NM_001130977.2:c.265C>T
NM_001130978.2:c.265C>T
NM_001130979.2:c.265C>T
NM_001130980.2:c.265C>T
NM_001130981.2:c.265C>T
NM_001130982.2:c.268C>T
NM_001130983.2:c.268C>T
NM_001130984.2:c.268C>T
NM_001130985.2:c.268C>T
NM_001130986.2:c.268C>T
NM_003494.4:c.265C>T

Pathogenic

Met criteria codes 4

PM3 PP4_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.265C>T p.(Arg89Ter) variant in DYSF, which is also known as NM_001130987.2: c.268C>T (p.Arg90Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 4/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been identified in at least five unrelated individuals with features consistent with LGMD (PMID: 23641709; 18853459; 21173544; 19493611), including in a homozygous state in two patients, one with known familial consanguinity (0.75 pts, PMID: 18853459; 19493611). It has also been observed in unknown phase with a pathogenic variant (NM_003494.4: c.3126G>A p.(Trp1042Ter), 0.5 pts, PMID: 18853459) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PMID: 18853459; 19493611; PP4_Strong). The highest population minor allele frequency is 0.00005974 in gnomAD v4.1.0 exomes (2/33480 African/African American chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting 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; 04/16/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3	✔	This variant has been identified in at least five unrelated individuals with features consistent with LGMD (PMID: 23641709, 18853459, 21173544, 19493611), including in a homozygous state in two patients, one with known familial consanguinity (0.75 pts, PMID: 18853459, 19493611). It has also been observed in unknown phase with a pathogenic variant (NM_003494.4: c.3126G>A p.(Trp1042Ter), 0.5 pts, PMID: 18853459) (PM3). The classification of c.3126G>A p.(Trp1042Ter) as Pathogenic has been approved and did not make use of this case.

PP4_Strong	ℹ	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and severely reduced or absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PMID: 18853459, 19493611; PP4_Strong).
PVS1	ℹ	✔	The NM_003494.4: c.265C>T p.(Arg89Ter) variant in DYSF, which is also known as NM_001130987.2: c.268C>T (p.Arg90Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 4/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting	ℹ	✔	The highest population minor allele frequency is 0.00005974 in gnomAD v4.1.0 exomes (2/33480 African/African American chromosomes), which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). Note: PM2_Supporting is still met if the FAF is calculated for the European (non-Finnish) exome data (4/1111974 exome alleles = FAF of 0.000008)

Curation History

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