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Variant: NM_001130987.2(DYSF):c.1225C>T (p.Arg409Ter)

Version: 1.0

CA1705654

265487 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 07b0d7cb-9a41-40f0-a2a3-3665888ce2f6
Approved on: 2026/5/1
Published on: 2026/5/7

HGVS expressions

NM_001130987.2:c.1225C>T
NM_001130987.2(DYSF):c.1225C>T (p.Arg409Ter)
NC_000002.12:g.71526295C>T
CM000664.2:g.71526295C>T
NC_000002.11:g.71753425C>T
CM000664.1:g.71753425C>T
NC_000002.10:g.71606933C>T
NG_008694.1:g.77673C>T
ENST00000258104.8:c.1129C>T
ENST00000410020.8:c.1225C>T
ENST00000258104.7:c.1129C>T
ENST00000394120.6:c.1132C>T
ENST00000409366.5:c.1132C>T
ENST00000409582.7:c.1222C>T
ENST00000409651.5:c.1225C>T
ENST00000409744.5:c.1132C>T
ENST00000409762.5:c.1222C>T
ENST00000410020.7:c.1225C>T
ENST00000410041.1:c.1225C>T
ENST00000413539.6:c.1222C>T
ENST00000429174.6:c.1129C>T
NM_001130455.1:c.1132C>T
NM_001130976.1:c.1129C>T
NM_001130977.1:c.1129C>T
NM_001130978.1:c.1129C>T
NM_001130979.1:c.1222C>T
NM_001130980.1:c.1222C>T
NM_001130981.1:c.1222C>T
NM_001130982.1:c.1225C>T
NM_001130983.1:c.1132C>T
NM_001130984.1:c.1132C>T
NM_001130985.1:c.1225C>T
NM_001130986.1:c.1132C>T
NM_001130987.1:c.1225C>T
NM_003494.3:c.1129C>T
NM_001130455.2:c.1132C>T
NM_001130976.2:c.1129C>T

NM_001130977.2:c.1129C>T
NM_001130978.2:c.1129C>T
NM_001130979.2:c.1222C>T
NM_001130980.2:c.1222C>T
NM_001130981.2:c.1222C>T
NM_001130982.2:c.1225C>T
NM_001130983.2:c.1132C>T
NM_001130984.2:c.1132C>T
NM_001130985.2:c.1225C>T
NM_001130986.2:c.1132C>T
NM_003494.4:c.1129C>T

Pathogenic

Met criteria codes 2

PP4_Strong PVS1

Not Met criteria codes 3

PM3 PM2 PP1

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 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_003494.4: c.1129C>T p.(Arg377Ter) variant in DYSF, which is also known as NM_001130987.2: c.1225C>T p.(Arg409Ter), is a nonsense variant that introduces a premature stop codon in exon 12/55, 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 three unrelated individuals with LGMD (PMID: 33250842, 22297152; ClinVar SCV004292580.2 internal data communication), including in unconfirmed phase with a presumed diagnostic variant in two patients and in a homozygous state in one patient with possible familial consanguinity (0.25 pts, PMID: 33250842). At least one patient homozygous for this variant showed both progressive proximal muscle weakness and absent dysferlin expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 33250842; PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.00017529 in gnomAD v4.1.0 (5/60010 Admixed American alleles), which is greater than the threshold for PM2_Supporting (criterion 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 LGMD VCEP (specifications v2.0.0; 05/01/2026): PVS1, PP4_Strong.

Met criteria codes

PP4_Strong	✔	At least one patient homozygous for this variant showed both progressive proximal muscle weakness and absent dysferlin expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 33250842; PP4_Strong).
PVS1	✔	The NM_003494.4: c.1129C>T p.(Arg377Ter) variant in DYSF, which is also known as NM_001130987.2: c.1225C>T p.(Arg409Ter), is a nonsense variant that introduces a premature stop codon in exon 12/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Not Met criteria codes

PM3	✖	This variant has been reported in at least three unrelated individuals with LGMD (PMID: 33250842, 22297152; ClinVar SCV004292580.2 internal data communication), including in unconfirmed phase with a presumed diagnostic variant in two patients and in a homozygous state in one patient with possible familial consanguinity (0.25 pts, PMID: 33250842). LOVD DYSF_000796: 2 single hits in Nallamilli et al. additional weight from PM3 not need for P classification
PM2	✖	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.00017529 in gnomAD v4.1.0 (5/60010 Admixed American alleles), which is greater than the threshold for PM2_Supporting (criterion not met).
PP1	✖	Likely one affected family member with the same genotype, but phase not confirmed (ClinVar SCV004292580.2 internal data communication).

Curation History

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