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Variant: NM_001130987.2(DYSF):c.4144C>T (p.Gln1382Ter)

Version: 1.0

CA10603803

281072 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d5db42f2-a0d3-4284-bb01-c5d21d8fb8b8
Approved on: 2025/4/21
Published on: 2025/5/16

HGVS expressions

NM_001130987.2:c.4144C>T
NM_001130987.2(DYSF):c.4144C>T (p.Gln1382Ter)
NC_000002.12:g.71611549C>T
CM000664.2:g.71611549C>T
NC_000002.11:g.71838679C>T
CM000664.1:g.71838679C>T
NC_000002.10:g.71692187C>T
NG_008694.1:g.162927C>T
ENST00000698057.1:c.1558C>T
ENST00000698058.1:c.775C>T
ENST00000698059.1:c.733C>T
ENST00000258104.8:c.4090C>T
ENST00000410020.8:c.4144C>T
ENST00000258104.7:c.4090C>T
ENST00000394120.6:c.4093C>T
ENST00000409366.5:c.4093C>T
ENST00000409582.7:c.4141C>T
ENST00000409651.5:c.4186C>T
ENST00000409744.5:c.4051C>T
ENST00000409762.5:c.4141C>T
ENST00000410020.7:c.4144C>T
ENST00000410041.1:c.4144C>T
ENST00000413539.6:c.4183C>T
ENST00000429174.6:c.4090C>T
ENST00000468173.1:n.326C>T
ENST00000472873.5:n.474C>T
ENST00000479049.6:n.975C>T
ENST00000487180.5:n.309C>T
ENST00000494501.5:n.388C>T
NM_001130455.1:c.4093C>T
NM_001130976.1:c.4048C>T
NM_001130977.1:c.4048C>T
NM_001130978.1:c.4090C>T
NM_001130979.1:c.4183C>T
NM_001130980.1:c.4141C>T
NM_001130981.1:c.4141C>T
NM_001130982.1:c.4186C>T

NM_001130983.1:c.4093C>T
NM_001130984.1:c.4051C>T
NM_001130985.1:c.4144C>T
NM_001130986.1:c.4051C>T
NM_001130987.1:c.4144C>T
NM_003494.3:c.4090C>T
NM_001130455.2:c.4093C>T
NM_001130976.2:c.4048C>T
NM_001130977.2:c.4048C>T
NM_001130978.2:c.4090C>T
NM_001130979.2:c.4183C>T
NM_001130980.2:c.4141C>T
NM_001130981.2:c.4141C>T
NM_001130982.2:c.4186C>T
NM_001130983.2:c.4093C>T
NM_001130984.2:c.4051C>T
NM_001130985.2:c.4144C>T
NM_001130986.2:c.4051C>T
NM_003494.4:c.4090C>T

Pathogenic

Met criteria codes 4

PM3 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.4090C>T p.(Gln1364Ter) variant in DYSF, which is also known as NM_001130987.2: c.4144C>T (p.Gln1382Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 38/55, 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 two patients with features of LGMD (PMID: 30564623; 36983702; 24488599; 27602406; LOVD Individual #00219787), including confirmed in trans with a likely pathogenic or pathogenic variant in one patient (NM_003494.4: c.5296G>A p.(Glu1766Lys), 1.0 pt, PMID: 36983702; 24488599; 27602406) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent or severely reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong). The highest population allele frequency for this variant is 0.0000008474 (1/1180034 exome chromosomes) in the European (non-Finnish) population in gnomAD v4.1.0, 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; 04/21/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PM3	✔	This variant has been identified in at least two patients with features of LGMD (PMID: 30564623, 36983702, 24488599, 27602406, LOVD Individual #00219787), including confirmed in trans with a likely pathogenic or pathogenic variant in one patient (c.5296G>A p.(Glu1766Lys), 1.0 pt, PMID: 36983702, 24488599, 27602406) (PM3). c.5296G>A p.(Glu1766Lys) can be classified as LP without circularity no other independent cases in ClinVar
PVS1	✔	The NM_003494.4: c.4090C>T p.(Gln1364Ter) variant in DYSF, which is also known as NM_001130987.2: c.4144C>T (p.Gln1382Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 38/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The highest population minor allele frequency is 0.0000008474 (1/1180034 exome chromosomes) in the European (non-Finnish) population in gnomAD v4.1.0, which is less than the LGMD VCEP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Strong	✔	At least one individual with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and absent or severely reduced dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 36983702; PP4_Strong).

Curation History

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