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Variant: NM_001130987.2(DYSF):c.4414G>T (p.Glu1472Ter)

Version: 1.0

CA49780605

984123 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3df0d1e4-3510-46db-9a7c-12f1fa13a2f3
Approved on: 2025/6/24
Published on: 2025/7/8

HGVS expressions

NM_001130987.2(DYSF):c.4414G>T (p.Glu1472Ter)
NM_001130987.2:c.4414G>T
NC_000002.12:g.71613360G>T
CM000664.2:g.71613360G>T
NC_000002.11:g.71840490G>T
CM000664.1:g.71840490G>T
NC_000002.10:g.71693998G>T
NG_008694.1:g.164738G>T
ENST00000698057.1:c.1828G>T
ENST00000698058.1:c.1045G>T
ENST00000698059.1:c.1003G>T
ENST00000258104.8:c.4360G>T
ENST00000410020.8:c.4414G>T
ENST00000258104.7:c.4360G>T
ENST00000394120.6:c.4363G>T
ENST00000409366.5:c.4363G>T
ENST00000409582.7:c.4411G>T
ENST00000409651.5:c.4456G>T
ENST00000409744.5:c.4321G>T
ENST00000409762.5:c.4411G>T
ENST00000410020.7:c.4414G>T
ENST00000410041.1:c.4414G>T
ENST00000413539.6:c.4453G>T
ENST00000429174.6:c.4360G>T
ENST00000468173.1:n.596G>T
ENST00000479049.6:n.1245G>T
ENST00000487180.5:n.579G>T
NM_001130455.1:c.4363G>T
NM_001130976.1:c.4318G>T
NM_001130977.1:c.4318G>T
NM_001130978.1:c.4360G>T
NM_001130979.1:c.4453G>T
NM_001130980.1:c.4411G>T
NM_001130981.1:c.4411G>T
NM_001130982.1:c.4456G>T
NM_001130983.1:c.4363G>T
NM_001130984.1:c.4321G>T

NM_001130985.1:c.4414G>T
NM_001130986.1:c.4321G>T
NM_001130987.1:c.4414G>T
NM_003494.3:c.4360G>T
NM_001130455.2:c.4363G>T
NM_001130976.2:c.4318G>T
NM_001130977.2:c.4318G>T
NM_001130978.2:c.4360G>T
NM_001130979.2:c.4453G>T
NM_001130980.2:c.4411G>T
NM_001130981.2:c.4411G>T
NM_001130982.2:c.4456G>T
NM_001130983.2:c.4363G>T
NM_001130984.2:c.4321G>T
NM_001130985.2:c.4414G>T
NM_001130986.2:c.4321G>T
NM_003494.4:c.4360G>T

Pathogenic

Met criteria codes 4

PM3_Supporting 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.4360G>T p.(Glu1454Ter) variant in DYSF, which is also known as NM_001130987.2: c.4414G>T p.(Glu1472Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 40/55, 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 one individual with late-onset dysferlinopathy, where it was identified in unknown phase with a pathogenic variant (NM_003494.4: c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 27602406, 33610434, 33715265, 36983702; PM3_Supporting). In addition to a clinical diagnosis of LGMD, this patient had absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 33715265, 36983702, 33610434; PP4_Strong). The highest minor allele frequency of this variant in gnomAD v4.1.0 is 0.00003334 (2/59984 Admixed American alleles), which is less than the LGMD VCEP threshold for PM2_Supporting (0.0001), 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; 06/24/2025): PVS1, PM3_Supporting, PM2_Supporting, PP4_Strong.

Met criteria codes

PM3_Supporting ✔

This variant has been identified in one individual with late-onset dysferlinopathy, where it was identified in unknown phase with a pathogenic variant (NM_003494.4: c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 27602406, 33610434, 33715265, 36983702; PM3_Supporting). There are four publications that are all likely describing the same individual. c.4756C>T p.(Arg1586Ter) is independently classified as Pathogenic. The variants are predicted on different haplotypes in gnomAD v2.

PP4_Strong	✔	At least one individual with a clinical diagnosis of LGMD had this variant and a second presumed diagnostic DYSF variant as well as absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 33715265, 36983702, 33610434).
PVS1	✔	The NM_003494.4: c.4360G>T p.(Glu1454Ter) variant in DYSF, which is also known as NM_001130987.2: c.4414G>T p.(Glu1472Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 40/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The highest minor allele frequency of this variant in gnomAD v4.1.0 is 0.00003334 (2/59984 Admixed American alleles), which is less than the LGMD VCEP threshold for PM2_Supporting (0.0001), meeting this criterion (PM2_Supporting).

Curation History

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