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Variant: NM_001130987.2(DYSF):c.3672C>G (p.Tyr1224Ter)

Version: 1.0

CA347224046

2674975 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6e6e6740-be93-488b-bafb-1e6ba331bba6
Approved on: 2025/5/28
Published on: 2025/6/6

HGVS expressions

NM_001130987.2(DYSF):c.3672C>G (p.Tyr1224Ter)
NM_001130987.2:c.3672C>G
NC_000002.12:g.71598661C>G
CM000664.2:g.71598661C>G
NC_000002.11:g.71825791C>G
CM000664.1:g.71825791C>G
NC_000002.10:g.71679299C>G
NG_008694.1:g.150039C>G
ENST00000698057.1:c.1044C>G
ENST00000698058.1:c.261C>G
ENST00000698059.1:c.261C>G
ENST00000258104.8:c.3618C>G
ENST00000410020.8:c.3672C>G
ENST00000258104.7:c.3618C>G
ENST00000394120.6:c.3621C>G
ENST00000409366.5:c.3621C>G
ENST00000409582.7:c.3669C>G
ENST00000409651.5:c.3714C>G
ENST00000409744.5:c.3579C>G
ENST00000409762.5:c.3669C>G
ENST00000410020.7:c.3672C>G
ENST00000410041.1:c.3672C>G
ENST00000413539.6:c.3711C>G
ENST00000429174.6:c.3618C>G
ENST00000475076.5:n.446C>G
ENST00000479049.6:n.503C>G
ENST00000493767.1:n.339C>G
NM_001130455.1:c.3621C>G
NM_001130976.1:c.3576C>G
NM_001130977.1:c.3576C>G
NM_001130978.1:c.3618C>G
NM_001130979.1:c.3711C>G
NM_001130980.1:c.3669C>G
NM_001130981.1:c.3669C>G
NM_001130982.1:c.3714C>G
NM_001130983.1:c.3621C>G
NM_001130984.1:c.3579C>G

NM_001130985.1:c.3672C>G
NM_001130986.1:c.3579C>G
NM_001130987.1:c.3672C>G
NM_003494.3:c.3618C>G
NM_001130455.2:c.3621C>G
NM_001130976.2:c.3576C>G
NM_001130977.2:c.3576C>G
NM_001130978.2:c.3618C>G
NM_001130979.2:c.3711C>G
NM_001130980.2:c.3669C>G
NM_001130981.2:c.3669C>G
NM_001130982.2:c.3714C>G
NM_001130983.2:c.3621C>G
NM_001130984.2:c.3579C>G
NM_001130985.2:c.3672C>G
NM_001130986.2:c.3579C>G
NM_003494.4:c.3618C>G

Pathogenic

Met criteria codes 4

PVS1 PM3_Supporting PP4 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.3618C>G p.(Tyr1206Ter) variant in DYSF, which is also known as NM_001130987.2: c.3672C>G p.(Tyr1224Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 33/55, 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 individuals with features of LGMD, including in a homozygous state without reported familial consanguinity in one patient (0.5 pts, PMID: 30564623, LOVD Individual #00219431) and in unknown phase or confirmed in trans with a second presumed diagnostic DYSF variant in at least one patient (NM_003494.4: c.4439A>C p.(Lys1480Thr), PMID: 15827562, 30919934, LOVD Individual #00215274) (PM3_Supporting). At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness (PMID: 30919934; PP4). This variant is absent from gnomAD v4.1.0 (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; 05/28/2025): PVS1, PM3_Supporting, PP4, PM2_Supporting.

Met criteria codes

PVS1	✔	The NM_003494.4: c.3618C>G p.(Tyr1206Ter) variant in DYSF, which is also known as NM_001130987.2: c.3672C>G p.(Tyr1224Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 33/55,

leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

PM3_Supporting	✔	This variant has been identified in at least two individuals with features of LGMD, including in a homozygous state without reported familial consanguinity in one patient (0.5 pts, PMID: 30564623, LOVD Individual #00219431) and in unknown phase or confirmed in trans with a second presumed diagnostic DYSF variant in at least one patient (c.4439A>C p.(Lys1480Thr), PMID: 15827562, 30919934, LOVD Individual #00215274) (PM3_Supporting). PMIDs 15827562 and 30919934 seem likely to be reporting the same case, while LOVD Individual #00215274 seems likely to be different, but since they all have the same variants and I couldn't confirm, I reported as "at least one". c.4439A>C p.(Lys1480Thr) will most likely be classified as LP but also appears as part of a complex allele, so since we don't need the points to classify as P, I didn't award any.
PP4	✔	At least one patient with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness (PMID: 30919934; PP4). It seems quite likely that the patient with near-absent dysferlin protein expression in skeletal muscle but no clinical details reported by Huang et al. is the same as the patient with progressive limb girdle muscle weakness reported in Ten Dam et al., but without being able to confirm, opted to stick at Supporting since a Pathogenic classification still reached.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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