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Variant: NM_001130987.2(DYSF):c.3498_3499delinsAA (p.Tyr1166_Gly1167delinsTer)

Version: 1.0

CA222156

94305 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 87f393fa-1b09-4af4-9687-8ee3aa108b19
Approved on: 2026/1/23
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HGVS expressions

NM_001130987.2(DYSF):c.3498_3499delinsAA (p.Tyr1166_Gly1167delinsTer)
NM_001130987.2:c.3498_3499delinsAA
NC_000002.12:g.71590212_71590213delinsAA
CM000664.2:g.71590212_71590213delinsAA
NC_000002.11:g.71817342_71817343delinsAA
CM000664.1:g.71817342_71817343delinsAA
NC_000002.10:g.71670850_71670851delinsAA
NG_008694.1:g.141590_141591delinsAA
ENST00000698057.1:c.870_871delinsAA
ENST00000698058.1:c.87_88delinsAA
ENST00000698059.1:c.87_88delinsAA
ENST00000258104.8:c.3444_3445delinsAA
ENST00000410020.8:c.3498_3499delinsAA
ENST00000258104.7:c.3444_3445delinsAA
ENST00000394120.6:c.3447_3448delinsAA
ENST00000409366.5:c.3447_3448delinsAA
ENST00000409582.7:c.3495_3496delinsAA
ENST00000409651.5:c.3540_3541delinsAA
ENST00000409744.5:c.3405_3406delinsAA
ENST00000409762.5:c.3495_3496delinsAA
ENST00000410020.7:c.3498_3499delinsAA
ENST00000410041.1:c.3498_3499delinsAA
ENST00000413539.6:c.3537_3538delinsAA
ENST00000429174.6:c.3444_3445delinsAA
ENST00000475076.5:n.272_273delinsAA
ENST00000479049.6:n.329_330delinsAA
ENST00000493767.1:n.165_166delinsAA
NM_001130455.1:c.3447_3448delinsAA
NM_001130976.1:c.3402_3403delinsAA
NM_001130977.1:c.3402_3403delinsAA
NM_001130978.1:c.3444_3445delinsAA
NM_001130979.1:c.3537_3538delinsAA
NM_001130980.1:c.3495_3496delinsAA
NM_001130981.1:c.3495_3496delinsAA

NM_001130982.1:c.3540_3541delinsAA
NM_001130983.1:c.3447_3448delinsAA
NM_001130984.1:c.3405_3406delinsAA
NM_001130985.1:c.3498_3499delinsAA
NM_001130986.1:c.3405_3406delinsAA
NM_001130987.1:c.3498_3499delinsAA
NM_003494.3:c.3444_3445delinsAA
NM_001130455.2:c.3447_3448delinsAA
NM_001130976.2:c.3402_3403delinsAA
NM_001130977.2:c.3402_3403delinsAA
NM_001130978.2:c.3444_3445delinsAA
NM_001130979.2:c.3537_3538delinsAA
NM_001130980.2:c.3495_3496delinsAA
NM_001130981.2:c.3495_3496delinsAA
NM_001130982.2:c.3540_3541delinsAA
NM_001130983.2:c.3447_3448delinsAA
NM_001130984.2:c.3405_3406delinsAA
NM_001130985.2:c.3498_3499delinsAA
NM_001130986.2:c.3405_3406delinsAA
NM_003494.4:c.3444_3445delinsAA

Pathogenic

Met criteria codes 5

PM3_Strong PP4_Strong PVS1 PM2_Supporting 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.3444_3445delTGinsAA p.(Tyr1148Ter) variant in DYSF, which is also known as NM_001130987.2: c.3498_3499delinsAA p.(Tyr1166Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 32/55, 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 10 unrelated individuals with LGMD (PMID: 195280, 27066573, 27602406, 30564623) including in a homozygous state in four patients, which includes a sibling pair, all without reported familial consanguinity (1.0 pt, PMID: 15469449, 27602406) and in unknown phase with a pathogenic variant in one patient (c.6124C>T p.(Arg2042Cys), 0.5 pts, PMID: 27602406). The variant was also identified in two affected siblings in a confirmed trans phase with a pathogenic variant (c.4886+1249G>T, 1.0 pt, PMID: 30564623) (PM3_Strong; PP1). At least one of these patients had a clinical diagnosis of LGMD and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 27602406; PP4_Strong). While this variant is not called as an insertion-deletion in gnomAD v4.1.0, read data indicates the presence of both component single nucleotide variants in cis in multiple individuals. The frequency of one component variant, (c.3444T>A p.(Tyr1148Ter), is also below the LGMD VCEP threshold (≤0.0001) (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 (specifications v2.0.0; 01/23/2026): PVS1, PM3_Strong, PP4_Strong, PP1, PM2_supporting.

Met criteria codes

PM3_Strong	✔	This variant has been identified in at least 10 unrelated individuals with LGMD (PMID: 195280, 27066573, 27602406, 30564623) including in a homozygous state in four patients, which includes a sibling pair, all without reported familial consanguinity (1.0 pt, PMID: 15469449, 27602406) and in unknown phase with a pathogenic variant in one patient (c.6124C>T p.(Arg2042Cys), 0.5 pts, PMID: 27602406). The variant was also identified in two affected siblings in a confirmed trans phase with a pathogenic variant (c.4886+1249G>T, 1.0 pt, PMID: 30564623) (PM3_Strong; PP1).
PP4_Strong	✔	At least one of the patients with two presumed diagnostic DYSF variants had a clinical diagnosis of LGMD and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 27602406; PP4_Strong).
PVS1	✔	The NM_003494.4: c.3444_3445delTGinsAA p.(Tyr1148Ter) variant in DYSF, which is also known as NM_001130987.2: c.3498_3499delinsAA p.(Tyr1166Ter), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 32/55, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). Splice AI: 0.66 (Acceptor gain) - out-of-frame
PM2_Supporting	✔	The filtering allele frequency of this variant is 0.000028251 in gnomAD v4.1.0 (the upper threshold of the 95% CI of 22/1112002 European (non-Finnish) exome chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). This variant is an MNV and the combined frequency is not present in gnomAD. However, the individual variants are present and the frequency was obtained from one of them (c.3444T>A p.(Tyr1148Ter)). Of note, available bam files show presence of both variants.
PP1	✔	This variant was identified in two sets of siblings, one in a homozygous state and the second in a compound heterozygous state with a pathogenic variant. Given PP4_Strong is applied, PP1 is capped at supporting.

Curation History

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