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Variant: NM_001130987.2(DYSF):c.5746T>C (p.Tyr1916His)

Version: 1.0

CA1707485

282408 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 415050f9-91f0-46ff-9526-a6ef4515f5b1
Approved on: 2026/4/30
Published on: 2026/5/7

HGVS expressions

NM_001130987.2(DYSF):c.5746T>C (p.Tyr1916His)
NM_001130987.2:c.5746T>C
NC_000002.12:g.71669708T>C
CM000664.2:g.71669708T>C
NC_000002.11:g.71896838T>C
CM000664.1:g.71896838T>C
NC_000002.10:g.71750346T>C
NG_008694.1:g.221086T>C
ENST00000698057.1:c.3160T>C
ENST00000698058.1:c.2377T>C
ENST00000698059.1:c.2485T>C
ENST00000258104.8:c.5629T>C
ENST00000410020.8:c.5746T>C
ENST00000258104.7:c.5629T>C
ENST00000394120.6:c.5632T>C
ENST00000409366.5:c.5695T>C
ENST00000409582.7:c.5743T>C
ENST00000409651.5:c.5725T>C
ENST00000409744.5:c.5653T>C
ENST00000409762.5:c.5680T>C
ENST00000410020.7:c.5746T>C
ENST00000410041.1:c.5683T>C
ENST00000413539.6:c.5722T>C
ENST00000429174.6:c.5692T>C
ENST00000479049.6:n.2514T>C
NM_001130455.1:c.5632T>C
NM_001130976.1:c.5587T>C
NM_001130977.1:c.5650T>C
NM_001130978.1:c.5692T>C
NM_001130979.1:c.5722T>C
NM_001130980.1:c.5680T>C
NM_001130981.1:c.5743T>C
NM_001130982.1:c.5725T>C
NM_001130983.1:c.5695T>C
NM_001130984.1:c.5653T>C
NM_001130985.1:c.5683T>C
NM_001130986.1:c.5590T>C

NM_001130987.1:c.5746T>C
NM_003494.3:c.5629T>C
NM_001130455.2:c.5632T>C
NM_001130976.2:c.5587T>C
NM_001130977.2:c.5650T>C
NM_001130978.2:c.5692T>C
NM_001130979.2:c.5722T>C
NM_001130980.2:c.5680T>C
NM_001130981.2:c.5743T>C
NM_001130982.2:c.5725T>C
NM_001130983.2:c.5695T>C
NM_001130984.2:c.5653T>C
NM_001130985.2:c.5683T>C
NM_001130986.2:c.5590T>C
NM_003494.4:c.5629T>C

Likely Pathogenic

Met criteria codes 3

PP3 PM2_Supporting PP4_Strong

Not Met criteria codes 3

PS3 PM3 PM5

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.5629T>C variant in DYSF, which is also known as NM_001130987.2: c.5746T>C p.(Tyr1916His), is a missense variant expected to cause the substitution of tyrosine for histidine at amino acid 1877, p.(Tyr1877His). This variant has been identified in at least three individuals with features consistent with LGMD (PMID: 34559919, 30564623; ClinVar SCV002975439.1, Jain Foundation Dysferlin Registry internal data communication; LOVD Individuals #00219617 and #00376017), including in unknown phase with a variant classified as at least likely pathogenic in one patient with progressive muscle weakness, elevated serum creatine kinase, and suspected Miyoshi myopathy (NM_003494.4: c.1278dup p.(Lys427GlufsTer47), 0.25 pts, ClinVar SCV002975439.1, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong, PM3_Supporting not met). In the second case, a second DYSF variant was not identified (PMID: 34559919, LOVD Individual #00376017). In the third individual, c.5629T>C p.(Tyr1877His) was identified in unknown phase with a pathogenic DYSF variant (NM_003494.4: c.1168G>A p.(Asp390Asn)), but this individual was also homozygous for a pathogenic variant in ANO5 (c.191dup p.(Asn64LysfsTer15), with limited phenotype detail provided (PMID: 30564623, LOVD Individual #00219617). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00000657 (3/1180038 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (<0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.891, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for autosomal recessive limb-girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications version 2.0.0; 04/30/2026): PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.891, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). SpliceAI: no splice effect.
PM2_Supporting	✔	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.00000657 (3/1180038 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (<0.0001) (PM2_Supporting).
PP4_Strong	✔	This variant has been identified in one individual with progressive muscle weakness, elevated serum creatine kinase, and suspected Miyoshi myopathy as well as absent dysferlin expression by blood monocyte assay, where it was identified in unconfirmed phase with a second presumed diagnostic DYSF variant (ClinVar SCV002975439.1, Jain Foundation Dysferlin Registry internal data communication; PP4_Strong).

Not Met criteria codes

PS3	✖	Not tested in Tominaga et al. (2022).
PM3	✖	This variant has been identified in at least three individuals with features consistent with LGMD (PMID: 34559919, 30564623; ClinVar SCV002975439.1, Jain Foundation Dysferlin Registry internal data communication; LOVD Individuals #00219617 and #00376017), including in unknown phase with a variant independently classified as likely pathogenic in one patient (NM_003494.4: c.1278dup p.(Lys427GlufsTer47), 0.25 pts, ClinVar SCV002975439.1, Jain Foundation Dysferlin Registry internal data communication). In another case, a second DYSF variant was not identified (PMID: 34559919, LOVD Individual #00376017). In the third individual, c.5629T>C p.(Tyr1877His) was identified in unknown phase with a pathogenic DYSF variant (NM_003494.4: c.1168G>A p.(Asp390Asn)), but this individual was also homozygous for a pathogenic variant in ANO5 (c.191dup p.(Asn64LysfsTer15), with limited phenotype detail provided (PMID: 30564623, LOVD Individual #00219617). Co-occurrence: c.1278dup p.(Lys427Glufs*47): not found in gnomAD v4.1.0 c.1168G>A p.(Asp390Asn): predicted on different haplotype in European (non-Finnish) Notes: NeuroMeGen, Hospital Clinico Santiago de Compostela: likely pathogenic, No contact information. Labcorp Genetics (formerly Invitae): VUS - included, 0.25 pts Eurofins Ntd Llc (ga): VUS - Nallamilli case that could not be scored no other cases in LOVD, literature
PM5	✖	No variants qualified.

Curation History

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