

Variant: NM_001130987.2(DYSF):c.851C>T (p.Thr284Met)

Version: 1.0

CA222210 [↗](#)

94358 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: dcb5cba5-9433-4e34-8772-e1eefcbe743d

Approved on: 2025/6/17

Published on: 2025/7/8

HGVS expressions

- NM_001130987.2:c.851C>T
- NM_001130987.2(DYSF):c.851C>T (p.Thr284Met)
- NC_000002.12:g.71515714C>T
- CM000664.2:g.71515714C>T
- NC_000002.11:g.71742844C>T
- CM000664.1:g.71742844C>T
- NC_000002.10:g.71596352C>T
- NG_008694.1:g.67092C>T
- ENST00000258104.8:c.755C>T
- ENST00000410020.8:c.851C>T
- ENST00000258104.7:c.755C>T
- ENST00000394120.6:c.758C>T
- ENST00000409366.5:c.758C>T
- ENST00000409582.7:c.848C>T
- ENST00000409651.5:c.851C>T
- ENST00000409744.5:c.758C>T
- ENST00000409762.5:c.848C>T
- ENST00000410020.7:c.851C>T
- ENST00000410041.1:c.851C>T
- ENST00000413539.6:c.848C>T
- ENST00000429174.6:c.755C>T
- NM_001130455.1:c.758C>T
- NM_001130976.1:c.755C>T
- NM_001130977.1:c.755C>T
- NM_001130978.1:c.755C>T
- NM_001130979.1:c.848C>T
- NM_001130980.1:c.848C>T
- NM_001130981.1:c.848C>T
- NM_001130982.1:c.851C>T
- NM_001130983.1:c.758C>T
- NM_001130984.1:c.758C>T
- NM_001130985.1:c.851C>T
- NM_001130986.1:c.758C>T
- NM_001130987.1:c.851C>T
- NM_003494.3:c.755C>T
- NM_001130455.2:c.758C>T
- NM_001130976.2:c.755C>T

NM_001130977.2:c.755C>T
NM_001130978.2:c.755C>T
NM_001130979.2:c.848C>T
NM_001130980.2:c.848C>T
NM_001130981.2:c.848C>T
NM_001130982.2:c.851C>T
NM_001130983.2:c.758C>T
NM_001130984.2:c.758C>T
NM_001130985.2:c.851C>T
NM_001130986.2:c.758C>T
NM_003494.4:c.755C>T

Pathogenic

Met criteria codes 5

PM3_Strong

PS3_Moderate

PP4_Strong

PP3

PM2_Supporting

Evidence Links 1

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.755C>T variant in DYSF, which is also known as NM_001130987.2: c.851C>T p.(Thr284Met), is a missense variant predicted to cause substitution of threonine by methionine at amino acid 252, p.(Thr252Met). This variant has been observed in at least 12 individuals with features consistent with LGMD (PMID: 30564623; 36575883; 34559919; 33927379; 27647186; 21522182; LOVD DYSF_000768), including in a homozygous state in at least two patients without reported familial consanguinity (1.0 pt; PMID: 36575883; 21522182) and in unknown phase with a pathogenic variant in at least two patients (NM_003494.4: c.3790_3797_del p.(Ser1264ValfsTer9), 0.5 pts, PMID: 34559919, LOVD Individual #00375911; NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 0.5 pts, PMID: 30564623, LOVD Individual #00221967) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD/Miyoshi myopathy and significantly reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PP4_Strong; PMID: 21522182). The highest population frequency for this variant in gnomAD v4.1.0 is 0.00004458 (2/44866 East Asian chromosomes), which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting and therefore meets this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Thr252Met protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3). In addition, the computational predictor REVEL gives a score of 0.926, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). 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; 06/17/2025): PM3_Strong, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM3_Strong



This variant has been observed in at least 12 individuals with features consistent with LGMD (PMID: 30564623; 36575883; 34559919; 33927379; 27647186; 21522182; LOVD DYSF_000768), including in a homozygous state in at

least two patients without reported familial consanguinity (1.0 pt; PMID: 36575883; 21522182) and in unknown phase with a pathogenic variant in at least two patients (NM_003494.4: c.3790_3797_del p.(Ser1264ValfsTer9), 0.5 pts, PMID: 34559919; LOVD Individual #00375911; NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 0.5 pts, PMID: 30564623; LOVD Individual #00221967) (PM3_Strong). when both variants present in gnomAD v2, confirmed variants in unknown phase not predicted on same haplotype

PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Thr252Met protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3).
			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Thr252Met protein did not reach the cell membrane PubMed:35028538 
PP4_Strong			At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD/Miyoshi myopathy and significantly reduced dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PP4_Strong; PMID: 21522182).
PP3			The computational predictor REVEL gives a score of 0.926, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3).
PM2_Supporting			The highest population frequency for this variant in gnomAD v4.1.0 is 0.00004458 (2/44866 East Asian chromosomes), which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). FAF based on European (non-Finnish) population data also meets criterion

Curation History

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