

*Variant: NM_001130987.2(DYSF):c.5561G>T
(p.Cys1854Phe)*

Version: 1.0

CA10604436 [↗](#)

283243 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 02bfa83a-8d9d-4595-8d97-8d1aaf09c933

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HGVS expressions

NM_001130987.2:c.5561G>T

NM_001130987.2(DYSF):c.5561G>T (p.Cys1854Phe)

NC_000002.12:g.71669126G>T

CM000664.2:g.71669126G>T

NC_000002.11:g.71896256G>T

CM000664.1:g.71896256G>T

NC_000002.10:g.71749764G>T

NG_008694.1:g.220504G>T

ENST00000698057.1:c.2975G>T

ENST00000698058.1:c.2192G>T

ENST00000698059.1:c.2300G>T

ENST00000258104.8:c.5444G>T

ENST00000410020.8:c.5561G>T

ENST00000258104.7:c.5444G>T

ENST00000394120.6:c.5447G>T

ENST00000409366.5:c.5510G>T

ENST00000409582.7:c.5558G>T

ENST00000409651.5:c.5540G>T

ENST00000409744.5:c.5468G>T

ENST00000409762.5:c.5495G>T

ENST00000410020.7:c.5561G>T

ENST00000410041.1:c.5498G>T

ENST00000413539.6:c.5537G>T

ENST00000429174.6:c.5507G>T

ENST00000479049.6:n.2329G>T

NM_001130455.1:c.5447G>T

NM_001130976.1:c.5402G>T

NM_001130977.1:c.5465G>T

NM_001130978.1:c.5507G>T

NM_001130979.1:c.5537G>T

NM_001130980.1:c.5495G>T

NM_001130981.1:c.5558G>T

NM_001130982.1:c.5540G>T

NM_001130983.1:c.5510G>T

NM_001130984.1:c.5468G>T

NM_001130985.1:c.5498G>T
NM_001130986.1:c.5405G>T
NM_001130987.1:c.5561G>T
NM_003494.3:c.5444G>T
NM_001130455.2:c.5447G>T
NM_001130976.2:c.5402G>T
NM_001130977.2:c.5465G>T
NM_001130978.2:c.5507G>T
NM_001130979.2:c.5537G>T
NM_001130980.2:c.5495G>T
NM_001130981.2:c.5558G>T
NM_001130982.2:c.5540G>T
NM_001130983.2:c.5510G>T
NM_001130984.2:c.5468G>T
NM_001130985.2:c.5498G>T
NM_001130986.2:c.5405G>T
NM_003494.4:c.5444G>T

Pathogenic

Met criteria codes 4

PM3_Strong

PS3_Moderate

PP4_Strong

PM2_Supporting

Not Met criteria codes 1

PP3

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.5444G>T variant in DYSF, which is also known as NM_001130987.2: c.5561G>T p.(Cys1854Phe), is a missense variant predicted to cause substitution of cysteine to phenylalanine at amino acid 1815, p.(Cys1815Phe). This variant has been observed in at least six individuals with clinically suspected LGMD with a second pathogenic variant in unknown phase in three individuals (NM_003494.4: c.755C>T p.(Thr252Met), 0.5 pts, PMID: 30564623; c.757C>T p.(Arg253Trp), 0.5 pts, PMID: 30564623, LOVD Individual #00222699; c.1180+5G>C, 0.5 pts, Jain Foundation Dysferlin Registry internal data communication) and in a homozygous state in one individual with no reported consanguinity (0.5 pts, PMID: 27647186) (PM3_Strong). At least one individual with suspected LGMD and two presumed diagnostic variants also had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID 20544924). The highest minor allele frequency for this variant is 0.0000008509 (1/1175292 chromosomes) in the European (non-Finnish) population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Cys1815Phe protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). The computational predictor REVEL gives a score of 0.61, which is below the LGMD VCEP threshold of ≥0.70 (PP3 not met). In summary, this variant is 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): PP4_Strong, PS3_Moderate, PM2_Supporting, PM3_Strong.

Met criteria codes

PM3_Strong			This variant has been observed in at least six individuals with clinical suspected LGMD with a second pathogenic variant in unknown phase in three individuals (c.755C>T p.(Thr252Met), 0.5 pts, PMID: 30564623; c.757C>T p.(Arg253Trp), 0.5 pts, PMID: 30564623, LOVD Individual #00222699; c.1180+5G>C, 0.5 pts, Jain Foundation Dysferlin Registry internal data communication) and in a homozygous state in one individual with no reported consanguinity (0.5 pts, PMID: 27647186) (PM3_Strong).
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Cys1815Phe protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong			At least one individual with suspected LGMD and two presumed diagnostic variants also had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PP4_Strong; PMID 20544924).
PM2_Supporting			The highest minor allele frequency for this variant is 0.0000008509 (1/1175292 chromosomes) in the European (non-Finnish) population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting).

Not Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.61, which is below the LGMD VCEP threshold of ≥ 0.70 (PP3 not met). Splice AI: 0.08
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Curation History

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