

Variant: NM_001130987.2(DYSF):c.1439T>C (p.Leu480Pro)

Version: 1.0

CA240279 [↗](#)

194354 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: bc127c18-25d1-4d0a-b5f5-fac87b2c8ab8

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HGVS expressions

NM_001130987.2(DYSF):c.1439T>C (p.Leu480Pro)
NM_001130987.2:c.1439T>C
NC_000002.12:g.71535079T>C
CM000664.2:g.71535079T>C
NC_000002.11:g.71762209T>C
CM000664.1:g.71762209T>C
NC_000002.10:g.71615717T>C
NG_008694.1:g.86457T>C
ENST00000258104.8:c.1343T>C
ENST00000410020.8:c.1439T>C
ENST00000258104.7:c.1343T>C
ENST00000394120.6:c.1346T>C
ENST00000409366.5:c.1346T>C
ENST00000409582.7:c.1436T>C
ENST00000409651.5:c.1439T>C
ENST00000409744.5:c.1346T>C
ENST00000409762.5:c.1436T>C
ENST00000410020.7:c.1439T>C
ENST00000410041.1:c.1439T>C
ENST00000413539.6:c.1436T>C
ENST00000429174.6:c.1343T>C
NM_001130455.1:c.1346T>C
NM_001130976.1:c.1343T>C
NM_001130977.1:c.1343T>C
NM_001130978.1:c.1343T>C
NM_001130979.1:c.1436T>C
NM_001130980.1:c.1436T>C
NM_001130981.1:c.1436T>C
NM_001130982.1:c.1439T>C
NM_001130983.1:c.1346T>C
NM_001130984.1:c.1346T>C
NM_001130985.1:c.1439T>C
NM_001130986.1:c.1346T>C
NM_001130987.1:c.1439T>C
NM_003494.3:c.1343T>C
NM_001130455.2:c.1346T>C
NM_001130976.2:c.1343T>C

NM_001130977.2:c.1343T>C
NM_001130978.2:c.1343T>C
NM_001130979.2:c.1436T>C
NM_001130980.2:c.1436T>C
NM_001130981.2:c.1436T>C
NM_001130982.2:c.1439T>C
NM_001130983.2:c.1346T>C
NM_001130984.2:c.1346T>C
NM_001130985.2:c.1439T>C
NM_001130986.2:c.1346T>C
NM_003494.4:c.1343T>C

Pathogenic

Met criteria codes 5

- PP3
- PM3
- PP4_Strong
- PS3_Moderate
- 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 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.1343T>C variant in DYSF, which is also known as NM_001130987.2: c.1439T>C p.(Leu480Pro), is a missense variant predicted to cause substitution of leucine by proline at amino acid 448, p.(Leu448Pro). This variant has been reported in at least five patients with suspected LGMD (PMID: 23519732, 27602406, 30564623), including in unknown phase with a pathogenic variant in two individuals (NM_003494.4: c.5836_5839del p.(Gln1946TrpfsTer19), 0.5 pts, PMID: 23519732; NM_003494.4: c.3444_3445delinsAA p.(Tyr1148Ter), 0.5 pts, PMID: 27602406) (PM3). At least one of these patients displayed progressive muscle weakness and reduced or absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 23519732, 27602406) (PP4_Strong). The filtering allele frequency of this variant is 0.000025627 (the upper bound of the 95% CI of 21/1180016 European (non-Finnish) chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu448Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). In addition, the computational predictor REVEL gives a score of 0.76, 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 2.0.0; 08/14/2025): PM3, PP4_Strong, PS3_Moderate, PM2_Supporting, PP3.

Met criteria codes

PP3



The computational predictor REVEL gives a score of 0.76, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3).

PM3



This variant has been reported in at least five patients with suspected LGMD (PMID: 23519732, 27602406, 30564623), including in unknown phase with a second pathogenic variant in two individuals (NM_003494.4: c.5836_5839del p.(Gln1946TrpfsTer19), 0.5 pts, PMID: 23519732; NM_003494.4: c.3444_3445delinsAA p.(Tyr1148Ter) , 0.5 pts, PMID: 27602406) (PM3). c.3444_3445delinsAA p.(Tyr1148Ter) is not called as an MNV in gnomAD. But the two component SNVs are predicted on a different haplotype from the curated variant in the European (non-Finnish) population. cannot check co-occurrence for c.5836_5839del because it is only in genomes in gnomAD v2 both variants are classified as P independent of their observation with this variant

PP4_Strong			At least one of the patients with this variant and a second presumed diagnostic DYSF variant displayed progressive muscle weakness and reduced or absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 23519732, 27602406) (PP4_Strong).
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu448Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PM2_Supporting			The filtering allele frequency of this variant is 0.000025627 (the upper bound of the 95% CI of 21/1180016 European (non-Finnish) chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting).

Curation History

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