

Variant: NM\_001130987.2(DYSF):c.404C>T (p.Pro135Leu)

Version: 1.0

CA1705344 [↗](#)

284579 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 611e901d-b443-4b62-af27-656f95f2ebab

**Approved on:** 2025/6/17

**Published on:** 2025/7/8

## HGVS expressions

**NM\_001130987.2(DYSF):c.404C>T (p.Pro135Leu)**

**NM\_001130987.2:c.404C>T**

NC\_000002.12:g.71511865C>T

CM000664.2:g.71511865C>T

NC\_000002.11:g.71738995C>T

CM000664.1:g.71738995C>T

NC\_000002.10:g.71592503C>T

NG\_008694.1:g.63243C>T

ENST00000258104.8:c.401C>T

ENST00000410020.8:c.404C>T

ENST00000258104.7:c.401C>T

ENST00000394120.6:c.404C>T

ENST00000409366.5:c.404C>T

ENST00000409582.7:c.401C>T

ENST00000409651.5:c.404C>T

ENST00000409744.5:c.404C>T

ENST00000409762.5:c.401C>T

ENST00000410020.7:c.404C>T

ENST00000410041.1:c.404C>T

ENST00000413539.6:c.401C>T

ENST00000429174.6:c.401C>T

NM\_001130455.1:c.404C>T

NM\_001130976.1:c.401C>T

NM\_001130977.1:c.401C>T

NM\_001130978.1:c.401C>T

NM\_001130979.1:c.401C>T

NM\_001130980.1:c.401C>T

NM\_001130981.1:c.401C>T

NM\_001130982.1:c.404C>T

NM\_001130983.1:c.404C>T

NM\_001130984.1:c.404C>T

NM\_001130985.1:c.404C>T

NM\_001130986.1:c.404C>T

NM\_001130987.1:c.404C>T

NM\_003494.3:c.401C>T

NM\_001130455.2:c.404C>T

NM\_001130976.2:c.401C>T

NM\_001130977.2:c.401C>T  
NM\_001130978.2:c.401C>T  
NM\_001130979.2:c.401C>T  
NM\_001130980.2:c.401C>T  
NM\_001130981.2:c.401C>T  
NM\_001130982.2:c.404C>T  
NM\_001130983.2:c.404C>T  
NM\_001130984.2:c.404C>T  
NM\_001130985.2:c.404C>T  
NM\_001130986.2:c.404C>T  
NM\_003494.4:c.401C>T

Likely Benign

Met criteria codes 1

BP2

Not Met criteria codes 5

BS3

BP4

PP4

PM3

PM2

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 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.401C>T variant in DYSF, which is also known as NM\_001130987.2: c.404C>T p.(Pro135Leu), is a missense variant predicted to cause substitution of proline by leucine at amino acid 134, p.(Pro134Leu). This variant has been observed in two individuals with features consistent with LGMD (PMID: 36983702; 23406536; 30564623; LOVD Individual #00222735); however, in both cases it was identified in cis with a null variant, including one classified as pathogenic by the ClinGen LGMD VCEP (NM\_003494.4: c.5022del p.(Phe1674LeufsTer48), PMID: 36983702) (BP2; PP4 and PM3 not applicable). The filtering allele frequency of this variant is 0.0001865 in gnomAD v4.1.0 genomes (the upper threshold of the 95% CI of 3/41580 African/African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2\_Supporting ( $\leq 0.0001$ ) (PM2 not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Pro134Leu protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538; BS3 not met). The computational predictor REVEL gives a score of 0.15, which is above the LGMD VCEP threshold of  $\leq 0.1$  for BP4 (criterion not met). In summary, this variant meets the criteria to be classified as Likely Benign 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): BP2.

Met criteria codes

|     |                                                                                   |                                                                                   |                                                                                                                                                                                                                                                                                               |
|-----|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BP2 |  |  | This variant has been observed in cis with the variant NM_003494.4: c.5022del p.(Phe1674LeufsTer48), which is classified as pathogenic by the ClinGen LGMD VCEP (PMID: 36983702) (BP2). In 2nd patient, apparently in cis with c.502del p.(Asp168MetfsTer59), which has not been curated yet. |
|-----|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                 |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BS3 |                                                                                     |  | Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Pro134Leu protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538).                                                        |
| BP4 |  |  | The computational predictor REVEL gives a score of 0.15, which is above the LGMD VCEP threshold of $\leq 0.1$ (BP4 not met).                                                                                                                                                                    |
| PP4 |  |  | While this variant has been observed in conjunction with a second DYSF variant in at least two patients with clinically suspected LGMD, this code was not applied given its occurrence in cis with a proven (classified by VCEP) or presumed (null variant not yet curated) pathogenic variant. |
| PM3 |  |  | While this variant has been observed in conjunction with a second DYSF variant in at least two patients with clinically suspected LGMD, this code was not applied given its occurrence in cis with a proven (classified by VCEP) or presumed (null variant not yet curated) pathogenic variant. |
| PM2 |                                                                                     |  | The filtering allele frequency of this variant is 0.0001865 (the upper threshold of the 95% CI of 3/41580 African/African American genome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold ( $\leq 0.0001$ ) (PM2 not met).                                 |

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