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Variant: NM_001130987.2(DYSF):c.1721T>C (p.Leu574Pro)

Version: 1.0

CA1705913

545009 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6daf3419-e631-44cd-a2c9-ca2cf04b1fc9
Approved on: 2026/1/23
Published on: 2026/2/17

HGVS expressions

NM_001130987.2(DYSF):c.1721T>C (p.Leu574Pro)
NM_001130987.2:c.1721T>C
NC_000002.12:g.71551635T>C
CM000664.2:g.71551635T>C
NC_000002.11:g.71778765T>C
CM000664.1:g.71778765T>C
NC_000002.10:g.71632273T>C
NG_008694.1:g.103013T>C
ENST00000258104.8:c.1667T>C
ENST00000410020.8:c.1721T>C
ENST00000258104.7:c.1667T>C
ENST00000394120.6:c.1670T>C
ENST00000409366.5:c.1670T>C
ENST00000409582.7:c.1718T>C
ENST00000409651.5:c.1763T>C
ENST00000409744.5:c.1628T>C
ENST00000409762.5:c.1718T>C
ENST00000410020.7:c.1721T>C
ENST00000410041.1:c.1721T>C
ENST00000413539.6:c.1760T>C
ENST00000429174.6:c.1667T>C
NM_001130455.1:c.1670T>C
NM_001130976.1:c.1625T>C
NM_001130977.1:c.1625T>C
NM_001130978.1:c.1667T>C
NM_001130979.1:c.1760T>C
NM_001130980.1:c.1718T>C
NM_001130981.1:c.1718T>C
NM_001130982.1:c.1763T>C
NM_001130983.1:c.1670T>C
NM_001130984.1:c.1628T>C
NM_001130985.1:c.1721T>C
NM_001130986.1:c.1628T>C
NM_001130987.1:c.1721T>C
NM_003494.3:c.1667T>C
NM_001130455.2:c.1670T>C
NM_001130976.2:c.1625T>C

NM_001130977.2:c.1625T>C
NM_001130978.2:c.1667T>C
NM_001130979.2:c.1760T>C
NM_001130980.2:c.1718T>C
NM_001130981.2:c.1718T>C
NM_001130982.2:c.1763T>C
NM_001130983.2:c.1670T>C
NM_001130984.2:c.1628T>C
NM_001130985.2:c.1721T>C
NM_001130986.2:c.1628T>C
NM_003494.4:c.1667T>C

Pathogenic

Met criteria codes 5

PP1 PP3 PP4_Strong PS3_Moderate PM3_Strong

Not Met criteria codes 1

PM2

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 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.1667T>C variant in DYSF, which is also known as NM_001130987.2: c.1721T>C p.(Leu574Pro), is a missense variant predicted to cause substitution of leucine by proline at amino acid 556, p.(Leu556Pro). This variant has been reported in at least 18 individuals with features of LGMD (PMID: 27647186, 3560664 34559919). At least 11 individuals were homozygous, including three siblings with known consanguinity (1.0 pt, PMID: 27647186, 3560664 34559919; PP1). It was also identified in trans phase with a pathogenic variant in one individual (NM_003494.4: c.6124C>T p.(Arg2042Cys), 1.0 pt, PMID: 33560664) (PM3_Strong). At least one of these patients with two presumed diagnostic variants and clinical features of LGMD had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PMID: 27647186, 33560664; PP4_Strong). The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003332 (8/44628 East Asian chromosomes), which is greater than the LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu556Pro 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 0.72, 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; 01/23/2026): PM3_Strong, PP4_Strong, PS3_Moderate, PP1, PP3.

Met criteria codes

PP1	✔	This variant has been reported in three siblings with known consanguinity. Given PP4_Strong is applied, PP1 is capped at supporting.
PP3	✔	

The computational predictor REVEL gives a score of 0.72, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Splice AI: 0.02

PP4_Strong	✔	At least one patient with two presumed diagnostic variants and clinical features of LGMD had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PMID: 27647186, 33560664; PP4_strong).
PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu556Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). Non-functional by both 2A and ICC assays. PubMed:35028538
PM3_Strong	✔	This variant has been reported in at least 18 individuals with features of LGMD (PMID: 27647186, 3560664 34559919), in a homozygous state in at least 11 individuals including three siblings with known consanguinity (1.0 pt, PMID: 27647186, 3560664 34559919) and in a trans phase with a pathogenic variant in one individual (c.6124C>T p.(Arg2042Cys), 1.0 pt, PMID: 33560664) PM3_Strong; PP1).

Not Met criteria codes

PM2	✖	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003332 (8/44628 East Asian chromosomes), which is greater than the LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met).

Curation History

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