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Variant: NM_001130987.2(DYSF):c.1061T>C (p.Leu354Pro)

Version: 1.0

CA1705600

551237 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: daeab130-6aa5-4dc5-b3a7-9bed5ac9f61a
Approved on: 2025/11/17
Published on: 2026/1/12

HGVS expressions

NM_001130987.2(DYSF):c.1061T>C (p.Leu354Pro)
NM_001130987.2:c.1061T>C
NC_000002.12:g.71520816T>C
CM000664.2:g.71520816T>C
NC_000002.11:g.71747946T>C
CM000664.1:g.71747946T>C
NC_000002.10:g.71601454T>C
NG_008694.1:g.72194T>C
ENST00000258104.8:c.965T>C
ENST00000410020.8:c.1061T>C
ENST00000258104.7:c.965T>C
ENST00000394120.6:c.968T>C
ENST00000409366.5:c.968T>C
ENST00000409582.7:c.1058T>C
ENST00000409651.5:c.1061T>C
ENST00000409744.5:c.968T>C
ENST00000409762.5:c.1058T>C
ENST00000410020.7:c.1061T>C
ENST00000410041.1:c.1061T>C
ENST00000413539.6:c.1058T>C
ENST00000429174.6:c.965T>C
NM_001130455.1:c.968T>C
NM_001130976.1:c.965T>C
NM_001130977.1:c.965T>C
NM_001130978.1:c.965T>C
NM_001130979.1:c.1058T>C
NM_001130980.1:c.1058T>C
NM_001130981.1:c.1058T>C
NM_001130982.1:c.1061T>C
NM_001130983.1:c.968T>C
NM_001130984.1:c.968T>C
NM_001130985.1:c.1061T>C
NM_001130986.1:c.968T>C
NM_001130987.1:c.1061T>C
NM_003494.3:c.965T>C
NM_001130455.2:c.968T>C
NM_001130976.2:c.965T>C

NM_001130977.2:c.965T>C
NM_001130978.2:c.965T>C
NM_001130979.2:c.1058T>C
NM_001130980.2:c.1058T>C
NM_001130981.2:c.1058T>C
NM_001130982.2:c.1061T>C
NM_001130983.2:c.968T>C
NM_001130984.2:c.968T>C
NM_001130985.2:c.1061T>C
NM_001130986.2:c.968T>C
NM_003494.4:c.965T>C

Pathogenic

Met criteria codes 4

PS3_Moderate PP4_Strong PP3 PM3_Strong

Not Met criteria codes 1

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 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.965T>C variant in DYSF, which is also known as NM_001130987.2: c.1061T>C p.(Leu354Pro), is a missense variant predicted to cause substitution of leucine to proline at amino acid 322, p.(Leu322Pro). This variant has been detected in at least 15 unrelated individuals with LGMD (PMID: 29138090, 25591676, 34559919, 27647186, 32576226, 32400077), including in unconfirmed phase with a pathogenic variant in at least 4 patients (NM_003494.3: c.3137G>A p.(Arg1046His), 0.5 pts, PMID: 32400077; c.5077C>T p.(Arg1693Trp), 0.5 pts, PMID: 32400077; c.1852G>A p.(Gly618Arg), 0.5 pts, PMID: 32400077; c.610C>T p.(Arg204Ter), 0.5 pts, PMID: 29138090) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 25591676; PP4_Strong). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003216 (8/44884 East Asian chromosomes), which is greater than the LGMD VCEP threshold (0.0001), not meeting this criterion (PM2_Supporting not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu322Pro 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 0.94, which is above the VCEP threshold (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; 11/17/2025): PM3_Strong, PP4_Strong, PS3_Moderate, PP3.

Met criteria codes

PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Leu322Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).

PP4_Strong		✔	At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD and absent dysferlin protein expression in skeletal muscle, which is highly specific for DYSF-associated LGMD (PMID: 25591676; PP4_Strong)
PP3		✔	The computational predictor REVEL gives a score of 0.94, which is above the VCEP threshold (PP3).
PM3_Strong		✔	This variant has been detected in at least 15 unrelated individuals with LGMD (PMID: 29138090, 25591676, 34559919, 27647186, 32576226, 32400077), including in unconfirmed phase with a pathogenic variant in at least 4 patients (NM_003494.3: c.3137G>A p.(Arg1046His), 0.5 pts, PMID: 32400077; c.5077C>T p.(Arg1693Trp), 0.5 pts, PMID: 32400077; c.1852G>A p.(Gly618Arg), 0.5 pts, PMID: 32400077; c.610C>T p.(Arg204Ter), 0.5 pts, PMID: 29138090) (PM3_Strong). Haplotype co-occurrence was checked for all scored variants in unconfirmed phase

Not Met criteria codes

PM2		✖	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003216 (8/44884 East Asian chromosomes), which is greater than the LGMD VCEP threshold (0.0001), not meeting this criterion (PM2_Supporting not met).

Curation History

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