The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001130987.2(DYSF):c.961T>C (p.Ser321Pro)

Version: 1.0

CA222222

94366 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d9612370-8c23-45d9-81eb-45986ae86bf9
Approved on: 2025/6/24
Published on: 2025/7/8

HGVS expressions

NM_001130987.2:c.961T>C
NM_001130987.2(DYSF):c.961T>C (p.Ser321Pro)
NC_000002.12:g.71516998T>C
CM000664.2:g.71516998T>C
NC_000002.11:g.71744128T>C
CM000664.1:g.71744128T>C
NC_000002.10:g.71597636T>C
NG_008694.1:g.68376T>C
ENST00000258104.8:c.865T>C
ENST00000410020.8:c.961T>C
ENST00000258104.7:c.865T>C
ENST00000394120.6:c.868T>C
ENST00000409366.5:c.868T>C
ENST00000409582.7:c.958T>C
ENST00000409651.5:c.961T>C
ENST00000409744.5:c.868T>C
ENST00000409762.5:c.958T>C
ENST00000410020.7:c.961T>C
ENST00000410041.1:c.961T>C
ENST00000413539.6:c.958T>C
ENST00000429174.6:c.865T>C
NM_001130455.1:c.868T>C
NM_001130976.1:c.865T>C
NM_001130977.1:c.865T>C
NM_001130978.1:c.865T>C
NM_001130979.1:c.958T>C
NM_001130980.1:c.958T>C
NM_001130981.1:c.958T>C
NM_001130982.1:c.961T>C
NM_001130983.1:c.868T>C
NM_001130984.1:c.868T>C
NM_001130985.1:c.961T>C
NM_001130986.1:c.868T>C
NM_001130987.1:c.961T>C
NM_003494.3:c.865T>C
NM_001130455.2:c.868T>C
NM_001130976.2:c.865T>C

NM_001130977.2:c.865T>C
NM_001130978.2:c.865T>C
NM_001130979.2:c.958T>C
NM_001130980.2:c.958T>C
NM_001130981.2:c.958T>C
NM_001130982.2:c.961T>C
NM_001130983.2:c.868T>C
NM_001130984.2:c.868T>C
NM_001130985.2:c.961T>C
NM_001130986.2:c.868T>C
NM_003494.4:c.865T>C

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PS3_Moderate | PM2_Supporting | PP3 | PP4

Not Met criteria codes 1

PM5

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.865T>C variant in DYSF, which is also known as NM_001130987.2: c.961T>C p.(Ser321Pro), is a missense variant predicted to cause substitution of serine by proline at amino acid 289, p.(Ser289Pro). This variant has been reported in two patients with features consistent with LGMD (PMID: 36983702; PMID: 30564623; LOVD DYSF_000780), including in unconfirmed phase with a pathogenic variant (NM_003494.4: c.757C>T p.(Arg253Trp), 0.5 pts; PMID: 0564623, LOVD Individual #00222734) (PM3_Supporting). One of the patients with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and reduced range dysferlin by blood monocyte assay (PP4; PMID: 36983702). The filtering allele frequency of this variant is 0.000007 in the European (non-Finnish) population of gnomAD v4.1.0 (the upper threshold of the 95% CI of 3/1112008 exome chromosomes), 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 Ser289Pro 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 0.71, 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 Likely 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 1.0.0; 06/24/2025): PM3_Supporting, PP4, PM2_Supporting, PS3_Moderate, PP3.

Met criteria codes

PM3_Supporting	✔	This variant has been reported in two patients with features consistent with LGMD (PMID: 36983702; PMID: 30564623; LOVD DYSF_000780), including in unconfirmed phase with a pathogenic variant (NM_003494.4: c.757C>T p.(Arg253Trp), 0.5 pts; PMID: 0564623, LOVD Individual #00222734) (PM3_Supporting). This variant not in gnomAD v2 and so cannot check co-occurrence data.

PS3_Moderate		✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Ser289Pro 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 0.000007 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/1112008 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PP3		✔	The computational predictor REVEL gives a score of 0.71, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).
PP4		✔	One of the patients with this variant and a second presumed diagnostic DYSF variant displayed progressive limb girdle muscle weakness and reduced range dysferlin by blood monocyte assay (PP4; PMID: 36983702).

Not Met criteria codes

PM5		✖	PM5 not likely c.866C>T p.(Ser289Phe), Variation ID: 287473, VUS by Emory, Labcorp/Invitae with no citations c.866C>G p.(Ser289Cys), Variation ID: 502094, VUS by 4 submitters, no citations

Curation History

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