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.2695A>C (p.Thr899Pro)

Version: 1.0

CA347214045

2674980 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: b32ec1c8-3d79-4df3-a953-4e8315a39deb
Approved on: 2026/4/30
Published on: 2026/5/7

HGVS expressions

NM_001130987.2(DYSF):c.2695A>C (p.Thr899Pro)
NM_001130987.2:c.2695A>C
NC_000002.12:g.71568080A>C
CM000664.2:g.71568080A>C
NC_000002.11:g.71795210A>C
CM000664.1:g.71795210A>C
NC_000002.10:g.71648718A>C
NG_008694.1:g.119458A>C
ENST00000698057.1:c.67A>C
ENST00000258104.8:c.2641A>C
ENST00000410020.8:c.2695A>C
ENST00000258104.7:c.2641A>C
ENST00000394120.6:c.2644A>C
ENST00000409366.5:c.2644A>C
ENST00000409582.7:c.2692A>C
ENST00000409651.5:c.2737A>C
ENST00000409744.5:c.2602A>C
ENST00000409762.5:c.2692A>C
ENST00000410020.7:c.2695A>C
ENST00000410041.1:c.2695A>C
ENST00000413539.6:c.2734A>C
ENST00000429174.6:c.2641A>C
NM_001130455.1:c.2644A>C
NM_001130976.1:c.2599A>C
NM_001130977.1:c.2599A>C
NM_001130978.1:c.2641A>C
NM_001130979.1:c.2734A>C
NM_001130980.1:c.2692A>C
NM_001130981.1:c.2692A>C
NM_001130982.1:c.2737A>C
NM_001130983.1:c.2644A>C
NM_001130984.1:c.2602A>C
NM_001130985.1:c.2695A>C
NM_001130986.1:c.2602A>C
NM_001130987.1:c.2695A>C
NM_003494.3:c.2641A>C
NM_001130455.2:c.2644A>C

NM_001130976.2:c.2599A>C
NM_001130977.2:c.2599A>C
NM_001130978.2:c.2641A>C
NM_001130979.2:c.2734A>C
NM_001130980.2:c.2692A>C
NM_001130981.2:c.2692A>C
NM_001130982.2:c.2737A>C
NM_001130983.2:c.2644A>C
NM_001130984.2:c.2602A>C
NM_001130985.2:c.2695A>C
NM_001130986.2:c.2602A>C
NM_003494.4:c.2641A>C

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PM3 PP4_Strong

Not Met criteria codes 3

PVS1 PM5 PS3

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.2641A>C variant in DYSF, which is also known as NM_001130987.2: c.2695A>C p.(Thr899Pro), is a missense variant predicted to cause substitution of threonine to proline at amino acid 881, p.(Thr881Pro). This variant has been observed in at least three individuals with suspected LGMD, including with a second pathogenic variant in unknown phase in two patients (NM_003494.4: c.907-3C>A, 0.5 pts, PMID: 24488599; c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 30564623; LOVD Individual #00221032; PM3). At least one patient with this variant and a second pathogenic DYSF variant had both clinical features of LGMD and absent dysferlin expression in muscle or blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 33927379, 24488599; PP4_Strong). The highest population allele frequency for this variant in gnomAD v4.1.0 is 0.00001667 (1/59986 Admixed American chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.74, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). This variant affects the last amino acid of exon 25, at the -3 position of the splice donor. Splice AI does not predict it will affect splicing, though a mini-gene assay has demonstrated that it results in partial skipping of exon 25, causing an in-frame deletion (PMID: 25312915; PVS1_RNA_Moderate not met). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed conflicting results for the Thr881Pro protein, which was classified as functional by 2-A assay but non-functional by immunofluorescence assay (PMID: 35028538; PS3_Moderate not met). In summary, this variant is 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 (specifications v2.0.0; 04/30/2026): PM3, PP4_Strong, PP3, PM2_Supporting.

Met criteria codes

PM2_Supporting ✔

The highest population allele frequency for this variant in gnomAD v4.1.0 is 0.00001667 (1/59986 Admixed American chromosomes), which is less than the threshold of 0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting).

PP3	✔	The computational predictor REVEL gives a score of 0.74, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). affects last amino acid of exon 25, at -3 position of splice donor Splice AI: 0.02 for acceptor loss; no effect on canonical donor
PM3	✔	This variant has been observed in at least three individuals with suspected LGMD, including with a second pathogenic variant in unknown phase in two patients (c.907-3C>A, 0.5 pts, PMID: 24488599; c.4756C>T p.(Arg1586Ter), 0.5 pts, PMID: 30564623; LOVD individual #00221032; PM3). absent from gnomAD v2 so co-occurrence cannot be assessed ClinVar: SCV006321740.1: LP by Revvity Omics, Revvity almost certainly reflects already scored LOVD Individual #00221032/case from Nallamilli (2018) SCV005422569.1: LP by Labcorp Women's Health no cases - carrier screening SCV004196526.1: LP by Baylor Genetics but communications with Baylor indicate this submission likely reflects carrier screening 2 patients in Dysferlin Registry with c.907-3C>A and c.1911C>A as second variants; considered duplicates of already-documented cases no other scoreable cases in LOVD curating c.1911C>A p.(Tyr637Ter) from PMID: 33927379 would be insufficient to upgrade PM3 strength or variant classification so not done at this time
PP4_Strong	✔	At least one patient with this variant and a second pathogenic DYSF variant had both clinical features of LGMD and absent dysferlin expression in muscle or blood monocytes, which is highly specific for DYSF-related LGMD (PMID: 33927379, 24488599; PP4_Strong).

Not Met criteria codes

PVS1	✖	A mini-gene assay has demonstrated that this variant results in partial skipping of exon 25, causing an in-frame deletion (PMID: 25312915; PVS1_RNA_Moderate not met). Since partial skipping is observed, PVS1_RNA is not being applied at any strength.
PM5	✖	Do not apply for missense variants encoded by the first or last 3 nucleotides of an exon unless a splice effect has been ruled out for the variant under curation and the variant(s) resulting in the same amino acid change. This variant affects the last amino acid of an exon. No other relevant missense changes at this position identified.
PS3	✖	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed conflicting results for the Thr881Pro protein, which was classified as functional by 2-A assay but non-functional by immunofluorescence assay (PMID: 35028538; PS3_Moderate not met).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.