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.1717C>T (p.Arg573Trp)

Version: 1.0

CA222133

94278 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: da132c96-8275-4add-9cd9-e5bd210d7405
Approved on: 2025/1/8
Published on: 2025/1/8

HGVS expressions

NM_001130987.2(DYSF):c.1717C>T (p.Arg573Trp)
NM_001130987.2:c.1717C>T
NC_000002.12:g.71551631C>T
CM000664.2:g.71551631C>T
NC_000002.11:g.71778761C>T
CM000664.1:g.71778761C>T
NC_000002.10:g.71632269C>T
NG_008694.1:g.103009C>T
ENST00000258104.8:c.1663C>T
ENST00000410020.8:c.1717C>T
ENST00000258104.7:c.1663C>T
ENST00000394120.6:c.1666C>T
ENST00000409366.5:c.1666C>T
ENST00000409582.7:c.1714C>T
ENST00000409651.5:c.1759C>T
ENST00000409744.5:c.1624C>T
ENST00000409762.5:c.1714C>T
ENST00000410020.7:c.1717C>T
ENST00000410041.1:c.1717C>T
ENST00000413539.6:c.1756C>T
ENST00000429174.6:c.1663C>T
NM_001130455.1:c.1666C>T
NM_001130976.1:c.1621C>T
NM_001130977.1:c.1621C>T
NM_001130978.1:c.1663C>T
NM_001130979.1:c.1756C>T
NM_001130980.1:c.1714C>T
NM_001130981.1:c.1714C>T
NM_001130982.1:c.1759C>T
NM_001130983.1:c.1666C>T
NM_001130984.1:c.1624C>T
NM_001130985.1:c.1717C>T
NM_001130986.1:c.1624C>T
NM_001130987.1:c.1717C>T
NM_003494.3:c.1663C>T
NM_001130455.2:c.1666C>T
NM_001130976.2:c.1621C>T

NM_001130977.2:c.1621C>T
NM_001130978.2:c.1663C>T
NM_001130979.2:c.1756C>T
NM_001130980.2:c.1714C>T
NM_001130981.2:c.1714C>T
NM_001130982.2:c.1759C>T
NM_001130983.2:c.1666C>T
NM_001130984.2:c.1624C>T
NM_001130985.2:c.1717C>T
NM_001130986.2:c.1624C>T
NM_003494.4:c.1663C>T

Pathogenic

Met criteria codes 5

PS3_Moderate PM3_Strong PP4_Strong PP1 PP3

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 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.1663C>T variant in DYSF, which is also known as NM_001130987.2: c.1717C>T p.(Arg573Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 555 (p.Arg555Trp). This variant has been detected in at least nine unrelated individuals with limb girdle muscular dystrophy (PMID: 16010686, 17698709, 18853459, 25591676, 25143362, 19015158), including in a homozygous state in two patients (0.75 pts, PMID: 25143362,16010686) and in trans with a pathogenic variant in at least two patients (c.3708delA p.(Asp1237ThrfsTer24), 1.0 pt, PMID: 19015158; c.3220_3221delCT p.(Leu1074PheTer39), 1.0 pt, PMID: 25591676) (PM3_Strong). At least one patient with this variant displayed progressive limb-girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16010686, 25143362, 19015158, 18853459). The variant has also been reported to segregate with LGMD in two affected family members from one family (PP1; PMID: 25143362). The filtering allele frequency of the variant is 0.0002685 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 3/28874), 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 Arg555Trp 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 exceeds the 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 1.0.0; 01/08/2025): PM3_Strong, PP4_Strong, PP1, PS3_Moderate, PP3.

Met criteria codes

PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg555Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).

Classified as non-functional in both assays PubMed:35028538

PM3_Strong	✔	This variant has been detected in at least nine unrelated individuals with limb girdle muscular dystrophy (PMID: 16010686, 17698709, 18853459, 25591676, 25143362, 19015158), including in a homozygous state in two patients (0.75 pts, PMID: 25143362,16010686) and in trans with a pathogenic variant in at least two patients (c.3708delA p.(Asp1237ThrfsTer24), 1.0 pt, PMID: 19015158; c.3220_3221delCT p.(Leu1074PheTer39), 1.0 pt, PMID: 25591676) (PM3_Strong).
PP4_Strong	✔	At least one patient with this variant displayed progressive limb-girdle muscle weakness and absent dysferlin protein expression, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 16010686, 25143362, 19015158, 18853459).
PP1	✔	The variant has also been reported to segregate with LGMD in two affected family members from one family (PP1; PMID: 25143362). (capped with PP4_Strong)
PP3	✔	The computational predictor REVEL gives a score of 0.94, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variant is 0.0002685 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 3/28874), which is greater than the LGMD VCEP threshold (<0.0001) (PM2_Supporting 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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.