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Variant: NM_001130987.2(DYSF):c.5149T>C (p.Cys1717Arg)

Version: 1.0

CA347220599

2674972 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 43b2838d-0637-4aac-a04f-99c529f22fcd
Approved on: 2026/1/23
Published on: 2026/2/17

HGVS expressions

NM_001130987.2(DYSF):c.5149T>C (p.Cys1717Arg)
NM_001130987.2:c.5149T>C
NC_000002.12:g.71664413T>C
CM000664.2:g.71664413T>C
NC_000002.11:g.71891543T>C
CM000664.1:g.71891543T>C
NC_000002.10:g.71745051T>C
NG_008694.1:g.215791T>C
ENST00000698057.1:c.2563T>C
ENST00000698058.1:c.1780T>C
ENST00000698059.1:c.1888T>C
ENST00000258104.8:c.5032T>C
ENST00000410020.8:c.5149T>C
ENST00000258104.7:c.5032T>C
ENST00000394120.6:c.5035T>C
ENST00000409366.5:c.5098T>C
ENST00000409582.7:c.5146T>C
ENST00000409651.5:c.5128T>C
ENST00000409744.5:c.5056T>C
ENST00000409762.5:c.5083T>C
ENST00000410020.7:c.5149T>C
ENST00000410041.1:c.5086T>C
ENST00000413539.6:c.5125T>C
ENST00000429174.6:c.5095T>C
ENST00000479049.6:n.1917T>C
NM_001130455.1:c.5035T>C
NM_001130976.1:c.4990T>C
NM_001130977.1:c.5053T>C
NM_001130978.1:c.5095T>C
NM_001130979.1:c.5125T>C
NM_001130980.1:c.5083T>C
NM_001130981.1:c.5146T>C
NM_001130982.1:c.5128T>C
NM_001130983.1:c.5098T>C
NM_001130984.1:c.5056T>C
NM_001130985.1:c.5086T>C
NM_001130986.1:c.4993T>C

NM_001130987.1:c.5149T>C
NM_003494.3:c.5032T>C
NM_001130455.2:c.5035T>C
NM_001130976.2:c.4990T>C
NM_001130977.2:c.5053T>C
NM_001130978.2:c.5095T>C
NM_001130979.2:c.5125T>C
NM_001130980.2:c.5083T>C
NM_001130981.2:c.5146T>C
NM_001130982.2:c.5128T>C
NM_001130983.2:c.5098T>C
NM_001130984.2:c.5056T>C
NM_001130985.2:c.5086T>C
NM_001130986.2:c.4993T>C
NM_003494.4:c.5032T>C

Pathogenic

Met criteria codes 5

PM5 PS3_Moderate PP4_Strong PP3 PM2_Supporting

Not Met criteria codes 1

PM3

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.5032T>C variant in DYSF, which is also known as NM_001130987.2: c.5149T>C p.(Cys1717Arg), is a missense variant predicted to cause substitution of cysteine to arginine at amino acid 1678, p.(Cys1678Arg). This variant has been observed in one individual with LGMD with a second variant in unknown phase. This individual also had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PMID: 25591676; PP4_Strong). The highest population frequency of this variant in gnomAD v4.1.0 is 0.00001098 in the South Asian population (1/91088 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 Cys1678Arg 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 0.95, which is above the LGMD VCEP threshold of ≥0.70 (PP3). In addition, two other missense variants at the same codon, NM_003494.4: c.5033G>A p.(Cys1678Tyr) and c.5033G>C p.(Cys1678Ser), have been classified as at least likely pathogenic by the ClinGen LGMD VCEP (PM5). In summary, this variant is classified as 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; 01/23/2026): PP4_Strong, PS3_Moderate, PM2_Supporting, PM5, PP3.

Met criteria codes

PM5	✔	Two other missense variants at the same codon, c.5033G>A p.(Cys1678Tyr) and c.5033G>C p.(Cys1678Ser), have been classified as at least likely pathogenic by the ClinGen LGMD VCEP (PM5). Both are LP without PM5 application.

Splice AI<0.5 for all variants

PS3_Moderate	✔	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Cys1678Arg protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP4_Strong	✔	Individual with clinical features of LGMD and two presumably diagnostic variants had absent dysferlin expression in muscle, which is highly specific for DYSF-related LGMD (PMID: 25591676; PP4_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.95, which is above the LGMD VCEP threshold of ≥0.70 (PP3). Splice AI: 0.14
PM2_Supporting	✔	The highest population frequency of this variant in gnomAD v4.1.0 is 0.00001098 in the South Asian population (1/91088 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Not Met criteria codes

PM3	✖	This variant has been observed in one individual with LGMD with a second variant in unknown phase (PMID: 25591676).

Curation History

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