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.3175C>T (p.Arg1059Cys)

Version: 1.0

CA1706454

286743 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4ec67d01-004b-4caf-9f85-df183fd6da2c
Approved on: 2026/4/28
Published on: 2026/5/7

HGVS expressions

NM_001130987.2:c.3175C>T
NM_001130987.2(DYSF):c.3175C>T (p.Arg1059Cys)
NC_000002.12:g.71570688C>T
CM000664.2:g.71570688C>T
NC_000002.11:g.71797818C>T
CM000664.1:g.71797818C>T
NC_000002.10:g.71651326C>T
NG_008694.1:g.122066C>T
ENST00000698057.1:c.547C>T
ENST00000258104.8:c.3121C>T
ENST00000410020.8:c.3175C>T
ENST00000258104.7:c.3121C>T
ENST00000394120.6:c.3124C>T
ENST00000409366.5:c.3124C>T
ENST00000409582.7:c.3172C>T
ENST00000409651.5:c.3217C>T
ENST00000409744.5:c.3082C>T
ENST00000409762.5:c.3172C>T
ENST00000410020.7:c.3175C>T
ENST00000410041.1:c.3175C>T
ENST00000413539.6:c.3214C>T
ENST00000429174.6:c.3121C>T
ENST00000461565.1:n.287C>T
NM_001130455.1:c.3124C>T
NM_001130976.1:c.3079C>T
NM_001130977.1:c.3079C>T
NM_001130978.1:c.3121C>T
NM_001130979.1:c.3214C>T
NM_001130980.1:c.3172C>T
NM_001130981.1:c.3172C>T
NM_001130982.1:c.3217C>T
NM_001130983.1:c.3124C>T
NM_001130984.1:c.3082C>T
NM_001130985.1:c.3175C>T
NM_001130986.1:c.3082C>T
NM_001130987.1:c.3175C>T
NM_003494.3:c.3121C>T

NM_001130455.2:c.3124C>T
NM_001130976.2:c.3079C>T
NM_001130977.2:c.3079C>T
NM_001130978.2:c.3121C>T
NM_001130979.2:c.3214C>T
NM_001130980.2:c.3172C>T
NM_001130981.2:c.3172C>T
NM_001130982.2:c.3217C>T
NM_001130983.2:c.3124C>T
NM_001130984.2:c.3082C>T
NM_001130985.2:c.3175C>T
NM_001130986.2:c.3082C>T
NM_003494.4:c.3121C>T

Likely Pathogenic

Met criteria codes 3

PP3 PM3 PP4_Strong

Not Met criteria codes 5

PM2 PM5 BS1 BS3 PS3

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 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.3121C>T variant in DYSF, which is also known as NM_001130987.2: c.3175C>T p.(Arg1059Cys), is a missense variant predicted to cause substitution of arginine to cysteine at amino acid 1041, p.(Arg1041Cys). This variant has been reported in at least four individuals with suspected LGMD including in a homozygous state in two individuals (1 pt, PMID: 15469449, 27602406) and with a second variant in unknown phase (c.2077delC p.(His693ThrfsTer4), 0.5 pts, PMID: 27602406) (PM3). The filtering allele frequency of this variant is 0.0002886 in gnomAD v4.1.1 (upper threshold of the 95% CI of 310/1179972 European (non-Finnish) chromosomes) which is greater than the ClinGen LGMD VCEP threshold (<0.0001) (PM2_Supporting and BS1 not applicable). The computational predictor REVEL gives a score of 0.82, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). At least one patient with suspected LGMD had this variant and a second presumed diagnostic DYSF variant and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 15469449, 27602406; PP4_Strong). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Arg1041Cys protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538; BS3 not met). 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 (specifications v2.0.0; 04/28/2026): PP4_strong, PM3, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.82, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). Splice AI: 0.00

PM3		✔	This variant has been reported in at least four individuals with suspected LGMD including in a homozygous state in two individuals (1 pt, PMID: 15469449, 27602406) and with a second variant in unknown phase (c.2077delC p.(His693ThrfsTer4), 0.5 pts, PMID: 27602406) (PM3).
PP4_Strong		✔	At least one patient with suspected LGMD had this variant and a second presumed diagnostic DYSF variant and absent dysferlin protein expression, which is highly specific for DYSF-related LGMD (PMID: 15469449, 27602406; PP4_Strong).

Not Met criteria codes

PM2		✖	The filtering allele frequency of this variant is 0.0002886 in gnomAD v4.1.1 (upper threshold of the 95% CI of 310/1179972 European (non-Finnish) chromosomes) which is greater than the ClinGen LGMD VCEP threshold (<0.0001) (PM2_Supporting and BS1 not applicable).
PM5		✖	Another missense variant at this position classified as VUS by VCEP (c.3122G>A p.(Arg1041His).
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed that the Arg1041Cys protein reached the cell membrane, indicating no significant impact on this aspect of protein function (PMID: 35028538; BS3 not met).
			Functional in both 2A and ICC assays of dysferlin membrane localization. BS3 not applicable. PubMed:35028538
PS3		✖	Functional in both 2A and ICC assays of dysferlin membrane localization. BS3 not applicable. PubMed:35028538

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.