

Variant: NM_001130987.2(DYSF):c.3172C>T (p.Arg1058Trp)

Version: 1.0

CA347217064 [↗](#)

498954 (ClinVar) [↗](#)

Gene: DYSF ([HGNC:8291](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: c7d03bd4-4885-42fd-932e-106122618165

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HGVS expressions

NM_001130987.2:c.3172C>T

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NC_000002.12:g.71570685C>T

CM000664.2:g.71570685C>T

NC_000002.11:g.71797815C>T

CM000664.1:g.71797815C>T

NC_000002.10:g.71651323C>T

NG_008694.1:g.122063C>T

ENST00000698057.1:c.544C>T

ENST00000258104.8:c.3118C>T

ENST00000410020.8:c.3172C>T

ENST00000258104.7:c.3118C>T

ENST00000394120.6:c.3121C>T

ENST00000409366.5:c.3121C>T

ENST00000409582.7:c.3169C>T

ENST00000409651.5:c.3214C>T

ENST00000409744.5:c.3079C>T

ENST00000409762.5:c.3169C>T

ENST00000410020.7:c.3172C>T

ENST00000410041.1:c.3172C>T

ENST00000413539.6:c.3211C>T

ENST00000429174.6:c.3118C>T

ENST00000461565.1:n.284C>T

NM_001130455.1:c.3121C>T

NM_001130976.1:c.3076C>T

NM_001130977.1:c.3076C>T

NM_001130978.1:c.3118C>T

NM_001130979.1:c.3211C>T

NM_001130980.1:c.3169C>T

NM_001130981.1:c.3169C>T

NM_001130982.1:c.3214C>T

NM_001130983.1:c.3121C>T

NM_001130984.1:c.3079C>T

NM_001130985.1:c.3172C>T

NM_001130986.1:c.3079C>T

NM_001130987.1:c.3172C>T

NM_003494.3:c.3118C>T

NM_001130455.2:c.3121C>T
NM_001130976.2:c.3076C>T
NM_001130977.2:c.3076C>T
NM_001130978.2:c.3118C>T
NM_001130979.2:c.3211C>T
NM_001130980.2:c.3169C>T
NM_001130981.2:c.3169C>T
NM_001130982.2:c.3214C>T
NM_001130983.2:c.3121C>T
NM_001130984.2:c.3079C>T
NM_001130985.2:c.3172C>T
NM_001130986.2:c.3079C>T
NM_003494.4:c.3118C>T

Pathogenic

Met criteria codes 6

- PM3_Supporting
- PP4_Strong
- PM2_Supporting
- PS3_Moderate
- PP1
- PP3

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.3118C>T variant in DYSF, which is also known as NM_001130987.2: c.3172C>T p.(Arg1058Trp), is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 1040, p.(Arg1040Trp). This variant has been reported in at least five individuals from four families with features overlapping LGMD (PMID: 27602406, 30564623, 30919934, 32400077), including in unknown phase with a second pathogenic variant in one individual (NM_003494.4: c.5979dup p.(Glu1994ArgfsTer3), 0.5 pts, PMID: 27602406; PM3_Supporting). At least one patient with this variant and another presumed diagnostic DYSF variant had clinical features of LGMD and absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 27602406; PP4_Strong). This variant has been observed to co-segregate with autosomal recessive LGMD in two affected family members (PMID: 30919934; PP1). The filtering allele frequency of this variant is 0.000085128 in gnomAD v4.1.0 (the upper threshold of the 95% CI of 3/91080 South Asian chromosomes), which is less than the ClinGen LGMD VCEP threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting). Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg1040Trp 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 0.81, 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 Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications version 2.0.0; 01/23/2026): PM3_Supporting, PP4_Strong, PS3_Moderate, PP3, PM2_Supporting, PP1.

Met criteria codes

PM3_Supporting  

This variant has been reported in at least five individuals from four families with features overlapping LGMD (PMID: 27602406, 30564623, 30919934, 32400077), including in unknown phase with a second pathogenic variant in one individual (c.5979dupA p.(Glu1994ArgfsTer3), 0.5 pts, PMID: 27602406; PM3_Supporting).

PP4_Strong			At least one patient with this variant and another presumed diagnostic DYSF variant had clinical features of LGMD and absent dysferlin expression in muscle biopsy, which is highly specific for DYSF-related LGMD (PMID: 27602406; PP4_Strong).
PM2_Supporting			The filtering allele frequency of this variant is 0.000085128 in gnomAD v4.1.0 (the upper threshold of the 95% CI of 3/91080 South Asian chromosomes), which is less than the ClinGen LGMD VCEP threshold for PM2_Supporting (<0.0001), meeting this criterion (PM2_Supporting).
PS3_Moderate			Immunofluorescence and 2-A assays of dysferlin membrane localization in HEK293T cells showed the Arg1040Trp protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP1			This variant has been observed to co-segregate with autosomal recessive LGMD in two affected family members (PMID: 30919934; PP1).
PP3			The computational predictor REVEL gives a score of 0.81, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3).

Curation History



 

 

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