

Variant: NM_001130987.2(DYSF):c.3167G>C (p.Arg1056Pro)

Version: 1.0

CA347217058 [↗](#)

2912979 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 01de1a33-69cc-420f-a15a-0bd913278275

Approved on: 2025/4/16

Published on: 2025/5/16

HGVS expressions

NM_001130987.2:c.3167G>C

NM_001130987.2(DYSF):c.3167G>C (p.Arg1056Pro)

NC_000002.12:g.71570680G>C

CM000664.2:g.71570680G>C

NC_000002.11:g.71797810G>C

CM000664.1:g.71797810G>C

NC_000002.10:g.71651318G>C

NG_008694.1:g.122058G>C

ENST00000698057.1:c.539G>C

ENST00000258104.8:c.3113G>C

ENST00000410020.8:c.3167G>C

ENST00000258104.7:c.3113G>C

ENST00000394120.6:c.3116G>C

ENST00000409366.5:c.3116G>C

ENST00000409582.7:c.3164G>C

ENST00000409651.5:c.3209G>C

ENST00000409744.5:c.3074G>C

ENST00000409762.5:c.3164G>C

ENST00000410020.7:c.3167G>C

ENST00000410041.1:c.3167G>C

ENST00000413539.6:c.3206G>C

ENST00000429174.6:c.3113G>C

ENST00000461565.1:n.279G>C

NM_001130455.1:c.3116G>C

NM_001130976.1:c.3071G>C

NM_001130977.1:c.3071G>C

NM_001130978.1:c.3113G>C

NM_001130979.1:c.3206G>C

NM_001130980.1:c.3164G>C

NM_001130981.1:c.3164G>C

NM_001130982.1:c.3209G>C

NM_001130983.1:c.3116G>C

NM_001130984.1:c.3074G>C

NM_001130985.1:c.3167G>C

NM_001130986.1:c.3074G>C

NM_001130987.1:c.3167G>C

NM_003494.3:c.3113G>C

NM_001130455.2:c.3116G>C
NM_001130976.2:c.3071G>C
NM_001130977.2:c.3071G>C
NM_001130978.2:c.3113G>C
NM_001130979.2:c.3206G>C
NM_001130980.2:c.3164G>C
NM_001130981.2:c.3164G>C
NM_001130982.2:c.3209G>C
NM_001130983.2:c.3116G>C
NM_001130984.2:c.3074G>C
NM_001130985.2:c.3167G>C
NM_001130986.2:c.3074G>C
NM_003494.4:c.3113G>C

Pathogenic

Met criteria codes 6

- PM3
- PM5
- PP4_Strong
- PM2_Supporting
- PS3_Moderate
- 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 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.3113G>C variant in DYSF, which is also known as NM_001130987.2: c.3167G>C p.(Arg1056Pro), is a missense variant predicted to cause substitution of arginine by proline at amino acid 1038, p.(Arg1038Pro). This variant has been reported in at least one individual with features consistent with LGMD, where it was confirmed in trans with a likely pathogenic or pathogenic variant (NM_003494.4: c.4756C>T p.(Arg1586Ter), 1.0 pt, PMID: 36983702, 33610434) (PM3). At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and absent dysferlin protein expression in both skeletal muscle and blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 33610434; 36983702). The filtering allele frequency of this variant is 0.000014124 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 9/1111952 European (non-Finnish) 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 Arg1038Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate). In addition, the computational predictor REVEL gives a score of 0.89, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to DYSF function (PP3). Another missense variant at the same codon, c.3113G>A p.(Arg1038Gln), has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). 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; 04/16/2025): PM3, PP4_Strong, PM2_Supporting, PS3_Moderate, PP3, PM5.

Met criteria codes

PM3			This variant has been reported in at least one individual with absent dysferlin protein expression and a diagnosis of Miyoshi myopathy, where it was confirmed in trans with a likely pathogenic or pathogenic variant (c.4756C>T p.(Arg1586Ter), 1.0 pt, PMID: 36983702, 33610434) (PM3). c.4756C>T p.(Arg1586Ter) can be classified as at least LP independently of this patient (PVS1, PM3 for 2 other patients)
PM5			Another missense variant at the same codon, c.3113G>A p.(Arg1038Gln), has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). The classification of c.3113G>A p.(Arg1038Gln) as Pathogenic has been approved by the VCEP, and PM5 was not applied for c.3113G>C p.(Arg1038Pro).
PP4_Strong			At least one patient with this variant and a second presumed diagnostic DYSF variant had a clinical diagnosis of LGMD (Miyoshi myopathy) and absent dysferlin protein expression in both skeletal muscle and blood monocytes, which is highly specific for DYSF-associated LGMD (PP4_Strong, PMID: 33610434, 36983702).
PM2_Supporting			The filtering allele frequency of this variant is 0.000014124 (the upper threshold of the 95% CI of 9/1111952 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, 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 Arg1038Pro protein did not reach the cell membrane, indicating an impact on protein function (PMID: 35028538) (PS3_Moderate).
PP3			The computational predictor REVEL gives a score of 0.89, 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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