Variant: NM_001130987.2(DYSF):c.1256G>C (p.Arg419Pro)

Version: 1.0

CA347213551

498211 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: cab3339e-49a5-40f2-876c-fde33f971d9b
Approved on: 2025-06-24
Published on: 2025-07-08

HGVS expressions

NM_001130987.2:c.1256G>C
NM_001130987.2(DYSF):c.1256G>C (p.Arg419Pro)
NC_000002.12:g.71526326G>C
CM000664.2:g.71526326G>C
NC_000002.11:g.71753456G>C
CM000664.1:g.71753456G>C
NC_000002.10:g.71606964G>C
NG_008694.1:g.77704G>C
ENST00000258104.8:c.1160G>C
ENST00000410020.8:c.1256G>C
ENST00000258104.7:c.1160G>C
ENST00000394120.6:c.1163G>C
ENST00000409366.5:c.1163G>C
ENST00000409582.7:c.1253G>C
ENST00000409651.5:c.1256G>C
ENST00000409744.5:c.1163G>C
ENST00000409762.5:c.1253G>C
ENST00000410020.7:c.1256G>C
ENST00000410041.1:c.1256G>C
ENST00000413539.6:c.1253G>C
ENST00000429174.6:c.1160G>C
NM_001130455.1:c.1163G>C
NM_001130976.1:c.1160G>C
NM_001130977.1:c.1160G>C
NM_001130978.1:c.1160G>C
NM_001130979.1:c.1253G>C
NM_001130980.1:c.1253G>C
NM_001130981.1:c.1253G>C
NM_001130982.1:c.1256G>C
NM_001130983.1:c.1163G>C
NM_001130984.1:c.1163G>C
NM_001130985.1:c.1256G>C
NM_001130986.1:c.1163G>C
NM_001130987.1:c.1256G>C
NM_003494.3:c.1160G>C
NM_001130455.2:c.1163G>C
NM_001130976.2:c.1160G>C

NM_001130977.2:c.1160G>C
NM_001130978.2:c.1160G>C
NM_001130979.2:c.1253G>C
NM_001130980.2:c.1253G>C
NM_001130981.2:c.1253G>C
NM_001130982.2:c.1256G>C
NM_001130983.2:c.1163G>C
NM_001130984.2:c.1163G>C
NM_001130985.2:c.1256G>C
NM_001130986.2:c.1163G>C
NM_003494.4:c.1160G>C

Uncertain Significance

Met criteria codes 4

PP4 PP3 PM3 PM2_Supporting

Not Met criteria codes 2

PM5 PS3

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.1160G>C variant in DYSF, which is also known as NM_001130987.2: c.1256G>C p.(Arg419Pro), is a missense variant predicted to cause substitution of arginine to proline at amino acid 387, p.(Arg387Pro). This variant has been reported in three patients with LGMD (PMID: 30564623, 39548682), including in an unknown phase with a pathogenic variant (c.2163-2A>G, 0.5 pts, PMID: 30564623, LOVD Individual #00222090) and in a homozygous state in two individuals, both with known consanguinity (0.25 pts for each patient; PMID: 39548682, LOVD Individuals #00392018, #00391975) (PM3; PP4). The highest minor allele frequency for this variant is 0.00002519 (1/39700 exome chromosomes) in the East Asian population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). In summary, due to insufficient evidence, this variant is classified as a variant of uncertain significance 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; 06/24/2025): PM2_Supporting, PM3, PP4, PP3.

Met criteria codes

PP4	✔	At least one patient with suspected LGMD had two presumably diagnostic variants. The GRASP participant who prompted this curation does not seem to have had a muscle biopsy; this could be a potential avenue to pursue to upgrade the classification.
PP3	✔	The computational predictor REVEL gives a score of 0.86, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3).

PM3		✔	This variant has been reported in three patients with LGMD (PMID: 30564623, 39548682), including in an unknown phase with a pathogenic variant (c.2163-2A>G, 0.5 pts, PMID: 30564623, LOVD Individual #00222090) and in a homozygous state in two individuals, both with known consanguinity (0.25 pts for each patient; PMID: 39548682, LOVD Individuals #00392018, #00391975) (PM3; PP4). No other cases in LOVD, and Eurofins Ntd Llc (ga) (Emory) is only submitter in ClinVar. Phasing was not done in the GRASP participant who prompted this curation (also reported in PMID: 30564623 and as LOVD Individual #00222090); confirming the variants were in trans would give us an additional 0.5 PM3 pts but would not be sufficient to upgrade to PM3_Strong.
PM2_Supporting		✔	The highest minor allele frequency for this variant is 0.00002519 (1/39700 exome chromosomes) in the East Asian population in gnomAD v4.1.0, which is less than the VCEP threshold of 0.0001 (PM2_Supporting).

Not Met criteria codes

PM5		✖	c.1160G<T p.(Arg387Leu) (Variation ID: 2441157) is VUS by Revvity and Ambry. No citations, not in LOVD. c.1160G>A p.(Arg387Gln) (Variation ID: 538630) is VUS by GeneDx and Natera and LB by Labcorp/Invitae. No citations, not in LOVD. c.1159C>T p.(Arg387Trp) (Variation ID: 287943) is VUS by 6 submitters and LB by 1. No citations aside from Nallamilli et al. (2018), who identified it 2x as a single hit per LOVD. No other cases in LOVD. None of the other missense variants at this position look common enough to have BS1 apply but also don't seem likely to reach LP.
PS3		✖	Not in the Tominaga et al. paper. No functional studies

Curation History

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