

Variant: *NM\_000070.3(CAPN3):c.1342C>T (p.Arg448Cys)*

Version: 1.0

CA7511324 [↗](#)

280038 (ClinVar) [↗](#)

**Gene:** CAPN3 ([HGNC:825](#))

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 572c20a5-4352-4af4-86df-93d13df66327

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### *HGVS expressions*

**NM\_000070.3:c.1342C>T**

**NM\_000070.3(CAPN3):c.1342C>T (p.Arg448Cys)**

NC\_000015.10:g.42399640C>T

CM000677.2:g.42399640C>T

NC\_000015.9:g.42691838C>T

CM000677.1:g.42691838C>T

NC\_000015.8:g.40479130C>T

NG\_008660.1:g.56538C>T

ENST00000349748.8:c.1198C>T

ENST00000357568.8:c.1342C>T

ENST00000397163.8:c.1342C>T

ENST00000466369.5:n.1851C>T

ENST00000483208.5:n.1573C>T

ENST00000495723.1:n.1573C>T

ENST00000549793.5:n.1573C>T

ENST00000638141.2:n.1213C>T

ENST00000673658.1:n.326C>T

ENST00000673705.1:c.297C>T

ENST00000318023.11:c.1198C>T

ENST00000349748.7:c.1198C>T

ENST00000357568.7:c.1342C>T

ENST00000397163.7:c.1342C>T

NM\_000070.2:c.1342C>T

NM\_024344.1:c.1342C>T

NM\_173087.1:c.1198C>T

NM\_024344.2:c.1342C>T

NM\_173087.2:c.1198C>T

**Pathogenic**

**Met criteria codes** 5

PM2\_Supporting

PP4\_Strong

PP3

PM5

PM3\_Strong

**Not Met criteria codes** 1

PS3

**Expert Panel**

Limb Girdle Muscular Dystrophy VCEP [↗](#)

**Criteria Specification Information**

[↗](#) **Criteria Specification:** ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP

Evidence submitted by expert panel

*Limb Girdle Muscular Dystrophy VCEP*

The NM\_000070.3: c.1342C>T variant in CAPN3 is a missense variant that results in the substitution of arginine with cysteine at codon 448, p.(Arg448Cys). This variant has been identified in at least nine individuals with clinical features consistent with limb-girdle muscular dystrophy (LGMD) (PMID: 37852290, 39733240, 16141003, 37526466, 17318636, 27447704, 18854869, 15221789, 17236769; GRASP-LGMD Consortium internal data communication), including in a homozygous state in at least four patients without reported familial consanguinity (1.0 pts; PMID: 16141003, 37526466, 17318636, 27447704, 18854869, 17236769). It has also been identified in unconfirmed phase with a pathogenic CAPN3 variant in at least two patients (c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 39733240; c.1115+5G>C, 0.5 pts, GRASP-LGMD Consortium internal data communication) (PM3\_Strong). At least one patient homozygous for this variant had both progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-associated LGMD (PMID: 18854869, 15221789; PP4\_Strong). The highest frequency for this variant in gnomAD v4.1.0 is 0.00003412 (2/58616 Admixed American chromosomes), which is lower than the ClinGen LGMD VCEP threshold of <0.0001 for PM2\_Supporting, meeting this criterion (PM2\_Supporting). The computational predictor REVEL gives a score of 0.846, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). In addition, another missense variant at the same codon, c.1343G>A p.(Arg448His), has been classified as pathogenic by the ClinGen LGMD VCEP (PM5). In summary, this variant meets 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 (version 2.0.0; 01/20/2026): PM3\_Strong, PP4\_Strong, PM2\_Supporting, PP3, PM5.

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM2_Supporting |  |  | The highest frequency for this variant in gnomAD v4.1.0 is 0.00003412 (2/58616 Admixed American chromosomes), which is lower than the ClinGen LGMD VCEP threshold of <0.0001 for PM2_Supporting, meeting this criterion (PM2_Supporting).                                                                                                                                                                                                                                                                                                                                |
| PP4_Strong     |  |  | At least one patient homozygous for this variant had both progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-associated LGMD (PMID: 18854869, 15221789; PP4_Strong).                                                                                                                                                                                                                                                                                                                 |
| PP3            |  |  | The computational predictor REVEL gives a score of 0.846, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI 0.06                                                                                                                                                                                                                                                                                                                                                                                   |
| PM5            |  |  | Another missense variant at the same codon, c.1343G>A p.(Arg448His), has been classified as pathogenic by the ClinGen LGMD VCEP (PM5). curated variant: Revel 0.846, spliceAI 0.06 comparison variants: c.1343G>T p.(Arg448Leu): curation in progress c.1343G>A p.(Arg448His): provisionally P without use of PM5; REVEL 0.904, spliceAI 0.01 Grantham Arg-Cys: 0.644 Arg-His: 0.567 Arg-Leu: 0.415 difference score for variant being curated is greater than that for P comparison variant, p.(Arg448His). code not needed for P classification but applies            |
| PM3_Strong     |  |  | This missense variant has been identified in at least nine individuals with clinical features consistent with limb-girdle muscular dystrophy (LGMD) (PMID: 37852290, 39733240, 16141003, 37526466, 17318636, 27447704, 18854869, 15221789, 17236769; GRASP-LGMD Consortium internal data communication), including in a homozygous state in at least four patients without reported familial consanguinity (1.0 pts; PMID: 16141003, 37526466, 17318636, 27447704, 18854869, 17236769). It has also been identified in unconfirmed phase with a pathogenic CAPN3 variant |

in at least two patients (c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 39733240; c.1115+5G>C, 0.5 pts, GRASP-LGMD Consortium internal data communication) (PM3\_Strong). co-occurrence checked for all scored variants in unconfirmed phase unscored cases: c.2362\_2363delinsTCA p.(Arg788SerfsTer13), which hasn't been curated yet but is on priority list for curation

Not Met criteria codes

PS3

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No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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