

Variant: *NM_000070.3(CAPN3):c.398C>T (p.Ala133Val)*

Version: 1.0

CA7511008 [↗](#)

290335 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ff47af5d-02a8-4524-adcf-652c03240ae4

Approved on: 2025/3/25

Published on: 2025/4/4

HGVS expressions

NM_000070.3(CAPN3):c.398C>T (p.Ala133Val)

NM_000070.3:c.398C>T

NC_000015.10:g.42386185C>T

CM000677.2:g.42386185C>T

NC_000015.9:g.42678383C>T

CM000677.1:g.42678383C>T

NC_000015.8:g.40465675C>T

NG_008660.1:g.43083C>T

ENST00000349748.8:c.398C>T

ENST00000357568.8:c.398C>T

ENST00000397163.8:c.398C>T

ENST00000466369.5:n.907C>T

ENST00000483208.5:n.629C>T

ENST00000495723.1:n.629C>T

ENST00000549793.5:n.629C>T

ENST00000638141.2:n.413C>T

ENST00000673705.1:c.70+1633C>T

ENST00000318023.11:c.398C>T

ENST00000349748.7:c.398C>T

ENST00000357568.7:c.398C>T

ENST00000397163.7:c.398C>T

NM_000070.2:c.398C>T

NM_024344.1:c.398C>T

NM_173087.1:c.398C>T

NM_024344.2:c.398C>T

NM_173087.2:c.398C>T

Uncertain Significance

Met criteria codes **3**

PM3_Strong

PP3

PP4

Not Met criteria codes **3**

BS2

PM2

PM5

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 CAPN3 Version 1.0.0

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.398C>T variant in CAPN3 is a missense variant predicted to cause substitution of alanine by valine at position 133, p.(Ala133Val). This variant has been reported in two unrelated individuals with a clinical diagnosis of LGMD, where it was confirmed in trans with a likely pathogenic or pathogenic variant (c.598_612del p.(Phe200_Leu204del), 1.0 pt x2, PMID: 16141003, LOVD individuals #00214184, #00214185; PM3_Strong, PP4). However, it has also been observed in a homozygous state or in trans with a second presumed diagnostic CAPN3 variant (c.133G>A p.(Ala45Thr), c.1303G>A (p.Glu435Lys)) in three individuals without a clear LGMD phenotype (ClinVar SCV001985435.3, SCV003509679.1 internal data communication). The filtering allele frequency of this variant is 0.0001855 (the upper threshold of the 95% CI of 16/86246 exome chromosomes) in the South Asian population in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met). Of note, the South Asian population also includes one homozygous individual of unknown age. The computational predictor REVEL gives a score of 0.959, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). In summary, while 6 Bayesian points were awarded to this variant based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (PM3_Strong, PP3, PP4), given the conflicting evidence, the VCEP has opted to classify it as a variant of uncertain significance for autosomal recessive limb girdle muscular dystrophy (LGMD VCEP specifications version 1.0.0; 03/25/2025).

Met criteria codes

PM3_Strong			This variant has been reported in at least two unrelated individuals with clinical features consistent with LGMD, where it was confirmed in trans with a likely pathogenic or pathogenic variant (c.598_612del p.(Phe200_Leu204del), 1.0 pt x2, PMID: 16141003, LOVD individuals #00214184, #00214185; PM3_Strong). However, it has also been observed in a homozygous state or in trans with a second presumed diagnostic CAPN3 variant (c.133G>A p.(Ala45Thr), c.1303G>A (p.Glu435Lys)) in three individuals without a clear LGMD phenotype (ClinVar SCV001985435.3, SCV003509679.1 internal data communication). No other scoreable cases in LOVD.
PP3			The computational predictor REVEL gives a score of 0.959, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function. SpliceAI 0.01
PP4			This variant has been reported with a second presumed diagnostic variant in CAPN3 in at least one individual with a clinical diagnosis of LGMD (PMID: 16141003, LOVD individuals #00214184, #00214185) (PP4).

Not Met criteria codes

BS2			1 homozygous individual of unknown age in gnomAD v4.1.0, but the VCEP has designated this code not applicable.
PM2			The filtering allele frequency of this variant is 0.0001855 (the upper threshold of the 95% CI of 16/86246 exome chromosomes) in the South Asian population in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001). In addition, the South Asian population also includes 1 homozygous individual of unknown age. Therefore, PM2_Supporting is not met for this variant.
PM5			

c.397G>A (p.Ala133Thr) is a mix of VUS/LP in ClinVar, seemingly relying heavily on internal Invitae/LabCorp internal data but at least one publication. c.397G>T (p.Ala133Ser) is a VUS with no literature cited. ClinVar SCV004698003.3 internal data communication: c.397G>A (p.Ala133Thr) identified in a homozygous state in a patient who presented with lower limb muscle weakness (clinically limb girdle) at age 35 who was also noted to have respiratory insufficiency At best, if c.397G>A (p.Ala133Thr) is classified as P (SpliceAI 0, Revel 0.91 scores meet criterion) PM5 could be applied, which would not change classification of c.398C>T (p.Ala133Val) (6 Bayesian points + 2 = 8, and it would remain at LP). Therefore, curation of c.397G>A (p.Ala133Thr) not pursued at this time.

Curation History [↗](#)

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