

Variant: *NM_000070.3(CAPN3):c.1250C>T (p.Thr417Met)*

Version: 1.0

CA7511300 [↗](#)

281505 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: cdc887b8-28d1-48c8-9b73-116f896e0f58

Approved on: 2025/5/3

Published on: 2025/6/6

HGVS expressions

NM_000070.3(CAPN3):c.1250C>T (p.Thr417Met)

NM_000070.3:c.1250C>T

NC_000015.10:g.42399548C>T

CM000677.2:g.42399548C>T

NC_000015.9:g.42691746C>T

CM000677.1:g.42691746C>T

NC_000015.8:g.40479038C>T

NG_008660.1:g.56446C>T

ENST00000349748.8:c.1106C>T

ENST00000357568.8:c.1250C>T

ENST00000397163.8:c.1250C>T

ENST00000466369.5:n.1759C>T

ENST00000483208.5:n.1481C>T

ENST00000495723.1:n.1481C>T

ENST00000549793.5:n.1481C>T

ENST00000638141.2:n.1121C>T

ENST00000673658.1:n.234C>T

ENST00000673705.1:c.205C>T

ENST00000318023.11:c.1106C>T

ENST00000349748.7:c.1106C>T

ENST00000357568.7:c.1250C>T

ENST00000397163.7:c.1250C>T

NM_000070.2:c.1250C>T

NM_024344.1:c.1250C>T

NM_173087.1:c.1106C>T

NM_024344.2:c.1250C>T

NM_173087.2:c.1106C>T

Pathogenic

Met criteria codes 3

PP4_Moderate PP3 PM3_Very
Strong

Not Met criteria codes 3

PS3 PM2 BP7

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.1250C>T variant in CAPN3 is a missense variant predicted to cause the substitution of threonine by methionine at codon 417, p.(Thr417Met). Across a selection of the available literature, this variant has been detected in at least seven individuals with features consistent with LGMD (PMID: 19556129, 27447704, 16650086, 37526466), including in a homozygous state in two patients without reported familial consanguinity (1.0 pt, PMID: 37526466) and confirmed in trans with a pathogenic variant in at least three patients (c.550del p.(Thr184ArgfsTer36) x2, 2.0 pts, PMID: 27447704, 37526466; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 1.0 pt, PMID: 16650086) (PM3_Very Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 16650086; PP4_Moderate). The filtering allele frequency of this variant is 0.0001353 (the upper threshold of the 95% CI of 130/1111468 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.90, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). A minigene assay showed the variant does not affect splicing (PMID: 32668095), consistent with the SpliceAI score of 0.02. In vitro evidence indicates that the p.Thr417Met amino acid change results in accelerated autoproteolysis, rendering the enzyme inactive prematurely (PMID: 19226146). 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; 05/03/2025): PM3_Very Strong, PP4_Moderate, PP3.

Met criteria codes

PP4_Moderate			At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 16650086; PP4_Moderate). PMID: 16650086 Krahn et al. (2006) patient 30: initially presented with LGMD and hyperCKemia, currently of moderate severity. Western blot results: 30 kDa severely decreased, 60 kDa normal, 94 kDa severely decreased. 2nd variant: c.1865_1866del p.(Glu622GlyfsTer9)
PP3			The computational predictor REVEL gives a score of 0.90, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3).
PM3_Very Strong			Across a selection of the available literature, this variant has been detected in at least seven individuals with features consistent with LGMD (PMID: 19556129, 27447704, 16650086, 37526466), including in a homozygous state in two patients without reported familial consanguinity (1.0 pt, PMID: 37526466) and confirmed in trans with a pathogenic variant in at least three patients (c.550del p.(Thr184ArgfsTer36) x2, 2.0 pts, PMID: 27447704, 37526466; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 1.0 pt, PMID: 16650086) (PM3_Very Strong).

Not Met criteria codes

PS3			In vitro evidence indicates that the p.Thr417Met amino acid change results in accelerated autoproteolysis, rendering the enzyme inactive prematurely (PMID: 19226146). However, this is not an approved assay.
PM2			

The filtering allele frequency of this variant is 0.0001353 (the upper threshold of the 95% CI of 130/1111468 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met).

BP7



This variant did not impact splicing when evaluated using a minigene assay (PMID: 32668095), but the high Revel score suggests the amino acid change may be relevant as a mechanism of disease. The variant is located well into the exon and has a SpliceAI score of 0.02.

Curation History [↗](#)

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Showing 1 to 1 of 1 rows

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