

Variant: *NM_000070.3(CAPN3):c.1505T>C (p.Ile502Thr)*

Version: 1.0

CA7511375 [↗](#)

282512 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: f77e66d1-d86f-4674-8e90-d2b2c50e7803

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HGVS expressions

NM_000070.3:c.1505T>C

NM_000070.3(CAPN3):c.1505T>C (p.Ile502Thr)

NC_000015.10:g.42401791T>C

CM000677.2:g.42401791T>C

NC_000015.9:g.42693989T>C

CM000677.1:g.42693989T>C

NC_000015.8:g.40481281T>C

NG_008660.1:g.58689T>C

ENST00000349748.8:c.1361T>C

ENST00000357568.8:c.1505T>C

ENST00000397163.8:c.1505T>C

ENST00000466369.5:n.2014T>C

ENST00000483208.5:n.1736T>C

ENST00000495723.1:n.1736T>C

ENST00000549793.5:n.1736T>C

ENST00000638141.2:n.1376T>C

ENST00000673705.1:c.309+2139T>C

ENST00000318023.11:c.1361T>C

ENST00000349748.7:c.1361T>C

ENST00000357568.7:c.1505T>C

ENST00000397163.7:c.1505T>C

NM_000070.2:c.1505T>C

NM_024344.1:c.1505T>C

NM_173087.1:c.1361T>C

NM_024344.2:c.1505T>C

NM_173087.2:c.1361T>C

Likely Pathogenic

Met criteria codes 4

PM3_Strong

PP1_Moderate

PP3

PP4_Moderate

Not Met criteria codes 2

PM5

PM2

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 2.0.0

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.1505T>C variant in CAPN3 is a missense variant predicted to cause the substitution of isoleucine by threonine at amino acid position 502 (p.Ile502Thr). This variant has been reported in at least 16 individuals with features of LGMD, including in trans with a pathogenic variant in one patient (c.1333G>A p.(Gly445Arg), 1.0 pt, PMID: 30919934, 10330340, LOVD Individual #00214106) and in unconfirmed phase with six unique pathogenic variants in 8 patients (c.146G>A, p.(Arg49His), 0.5 pts, ClinVar SCV000766735.7 internal data communication; c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00220543; c.598_612del p.(Phe200_Leu204del), 0.5 pts x2, PMID: 3056462, ClinVar SCV000612634.3 internal data communication; c.759_761del p.(Lys254del), 0.5 pts, ClinVar SCV000612634.3 internal data communication; c.643_663del p.(Ser215_Gly221del), 0.5 pts x2, ClinVar SCV000491158.7 internal data communication; c.145C>T (p.Arg49Cys), 0.5 pts, SCV000612634.3 internal data communication (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 in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 26810512; PP4_Moderate). The filtering allele frequency of this variant is 0.0005825 (the upper threshold of the 95% CI of 644/1179854 European (non-Finnish) chromosomes) in gnomAD v4.1.1, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.963, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). In summary, this variant meets the criteria to be classified as Likely Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP (specifications v2.0.0; 04/29/2026): PM3_Very Strong, PP4_Moderate, PP3.

Met criteria codes

PM3_Strong	 	This variant has been reported in at least 16 individuals with features of LGMD, including in trans with a pathogenic variant in one patient (c.1333G>A p.(Gly445Arg), 1.0 pt, PMID: 30919934, 10330340, LOVD Individual #00214106) and in unconfirmed phase with six unique pathogenic variants in 8 patients (c.146G>A, p.(Arg49His), 0.5 pts, ClinVar SCV000766735.7 internal data communication; c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00220543; c.598_612del p.(Phe200_Leu204del), 0.5 pts x2, PMID: 3056462, ClinVar SCV000612634.3 internal data communication; c.759_761del p.(Lys254del), 0.5 pts, ClinVar SCV000612634.3 internal data communication; c.643_663del p.(Ser215_Gly221del), 0.5 pts x2, ClinVar SCV000491158.7 internal data communication; c.145C>T (p.Arg49Cys), 0.5 pts, SCV000612634.3 internal data communication (PM3_Very Strong). If AD/AR included: 5 pts, PM3_Very Strong c.146G>A, p.(Arg49His), 0.5 pts, ClinVar SCV000766735.7 internal data communication c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00220543) c.598_612del15 p.(Phe200_Leu204del), 0.5 pts, PMID: 3056462 c.598_612del15 p.(Phe200_Leu204del), 0.5 pts, Athena/Quest c.1333G>A p.(Gly445Arg), 1.0 pt, PMID: 30919934, 10330340, LOVD Individual #00214106 c.759_761del p.(Lys254del), 0.5 pts, (Athena/Quest) c.643_663del21, (p.S215_G221del), 0.5 pts, GeneDx #1 c.643_663del21, (p.S215_G221del), 0.5 pts, GeneDx #2 c.145C>T (p.Arg49Cys), 0.5 pts, Athena/Quest If AD/AR not included: 1.5 pts, PM3 c.146G>A, p.(Arg49His), 0.5 pts, ClinVar SCV000766735.7 internal data communication c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00220543) c.145C>T(p.Arg49Cys), 0.5 pts, Athena/Quest AD/AR cases: up to 3.5 pts c.598_612del15 p.(Phe200_Leu204del) x2 (Athena/Quest, PMID: 3056462) c.1333G>A p.(Gly445Arg) x1 (PMID: 30919934, 10330340) c.759_761del(p.Lys254del) x1 (Athena/Quest) c.643_663del21, (p.S215_G221del) x2 (GeneDx) options for more PM3 pts in unknown phase with c.1745+5G>C (not yet curated, at best 0.5 pts): LP by Eurofins Ntd Llc, no citations in ClinVar, 1x in LOVD in unknown phase with c.802-9G>A (not yet curated, at best 0.5 pts): looks like clear P based on ClinVar c.1327T>C p.Ser443Pro x3, PMID: 26810512, 39258114, 35135626: VUS without evidence from cases with this variant
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PP1_Moderate

This variant co-segregated with autosomal recessive disease in two affected family members from one family (PMID: 30919934, 17562833).

PP3			The computational predictor REVEL gives a score of 0.963, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.00
PP4_Moderate			At least one patient with this variant and a second CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 26810512; PP4_Moderate). PMID: 26810512 Lahoria et al. (2016) patient 5: 48 year old male, exercise triggered 1 episode of rhabdomyolysis at 48 y with no preceding symptoms, elevated CK. at 23 y, clinical findings include proximal weakness with proximal myopathy with fibrillation potentials on EMG. Calpain-3 was reduced to less than 10% by Western blot of muscle biopsy, which also showed signs of myopathy. c.1327T>C p.Ser443Pro in unknown phase (LP without the data from this observation)

Not Met criteria codes

PM5			Another missense variant in CAPN3 affecting the same codon, c.1505T>G p.(Ile502Ser), is currently classified as VUS (PM5 not met).
PM2			The filtering allele frequency of this variant is 0.0005825 (the upper threshold of the 95% CI of 644/1179854 European (non-Finnish) chromosomes) in gnomAD v4.1.1, which is greater than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting not met).

Curation History

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Showing 1 to 1 of 1 rows

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