

Variant: NM_000070.3(CAPN3):c.1621C>T (p.Arg541Trp)

Version: 1.0

CA7511448 [↗](#)

498267 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

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HGVS expressions

NM_000070.3(CAPN3):c.1621C>T (p.Arg541Trp)

NM_000070.3:c.1621C>T

NC_000015.10:g.42402878C>T

CM000677.2:g.42402878C>T

NC_000015.9:g.42695076C>T

CM000677.1:g.42695076C>T

NC_000015.8:g.40482368C>T

NG_008660.1:g.59776C>T

ENST00000349748.8:c.1477C>T

ENST00000357568.8:c.1621C>T

ENST00000397163.8:c.1621C>T

ENST00000466369.5:n.2130C>T

ENST00000483208.5:n.2510C>T

ENST00000495723.1:n.2510C>T

ENST00000549793.5:n.1852C>T

ENST00000638141.2:n.1492C>T

ENST00000673646.1:c.85C>T

ENST00000673705.1:c.309+3226C>T

ENST00000673813.1:n.543C>T

ENST00000318023.11:c.1477C>T

ENST00000349748.7:c.1477C>T

ENST00000357568.7:c.1621C>T

ENST00000397163.7:c.1621C>T

ENST00000397200.8:c.85C>T

ENST00000567071.5:c.80C>T

ENST00000569827.5:c.85C>T

NM_000070.2:c.1621C>T

NM_024344.1:c.1621C>T

NM_173087.1:c.1477C>T

NM_173088.1:c.85C>T

NM_024344.2:c.1621C>T

NM_173087.2:c.1477C>T

NM_173088.2:c.85C>T

Pathogenic

PP1_Moderate PM3_Very Strong PP3
PP4 PM2_Supporting

Limb Girdle Muscular Dystrophy VCEP

Not Met criteria codes 1

PM5

Evidence Links 0

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
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.1621C>T variant in CAPN3 is a missense variant predicted to cause the substitution of tryptophan for arginine at position 541, p.(Arg541Trp). Across a selection of the available literature, this variant has been reported in at least 11 unrelated patients with features of LGMD (PMID: 19556129, 18854869, 32576226, 30919934, 25214167, 16100770, 36575883, 31066050), including in a homozygous state in two unrelated probands without reported consanguinity (0.5 pts x2; PMID: 31066050, 30919934), confirmed in trans with a pathogenic variant in three probands (c.701G>A p.(Gly234Glu), 1.0 pt, PMID: 3657588; c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 16100770; c.598_612del p.(Phe200_Leu204del), 1.0 pt, PMID: 16100770), and in unconfirmed phase with a pathogenic variant in two probands (c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 16100770; c.598_612del p.(Phe200_Leu204del), 0.5 pts, PMID: 18854869) (PM3_Very Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness (PP4). In addition, two affected family members of a homozygous proband were also shown to be homozygous for this variant (PMID: 30919934; PP1_Moderate). The highest population variant allele frequency in gnomAD v4.1.0 for is 0.00004455 (2/44898 East Asian chromosomes), which is is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.896, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function. 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 2.0.0; 12/29/2025): PM3_Very Strong, PP4, PP1_Moderate, PM2_Supporting, PP3.

Met criteria codes

PP1_Moderate			Two affected family members of a homozygous proband were also shown to be homozygous for this variant (PMID: 30919934; PP1_Moderate).
PM3_Very Strong			Across a selection of the available literature, this variant has been reported in at least 11 unrelated patients with features of LGMD (PMID: 19556129, 18854869, 32576226, 30919934, 25214167, 16100770, 36575883, 31066050), including in a homozygous state in two unrelated probands without reported consanguinity (0.5 pts x2; PMID: 31066050, 30919934), confirmed in trans with a pathogenic variant in three probands (c.701G>A p.(Gly234Glu), 1.0 pt, PMID: 3657588; c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 16100770; c.598_612del p.(Phe200_Leu204del), 1.0 pt, PMID: 16100770), and in unconfirmed phase with a pathogenic variant in two probands (c.550del p.(Thr184ArgfsTer36), 0.5 pts, PMID: 16100770; c.598_612del p.(Phe200_Leu204del), 0.5 pts, PMID: 18854869) (PM3_Very Strong). in gnomAD v2, predicted on a different haplotype from c.550del p.(Thr184ArgfsTer36) and c.598_612del p.(Phe200_Leu204del) In practice, only 0.5 pts out of the 4 needed for Very_Strong are coming from the c.598_612del p.(Phe200_Leu204del) proposed dominant variant, and it is for a family where the carrier parent was considered unaffected despite "special emphasis put on intensive search for new secondary cases in the family of the proband in order to determine the mode of inheritance" (PMID: 16100770). There are also unscored cases with presumed diagnostic variants that we haven't curated yet
PP3			

The computational predictor REVEL gives a score of 0.896, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function. 0.896

PP4			At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness (PP4). Note that Fanin et al. (2009) (PMID: 18854869) report absent calpain-3 protein expression in skeletal muscle by Western blot in a patient with a clinical diagnosis of LGMD, but the 2nd CAPN3 variant is c.598_612del in unknown phase, which is also a proposed AD. Because we don't really need this phenotype specificity evidence to reach P, I opted to apply PP1_Moderate for segregation evidence instead.
PM2_Supporting			The highest population variant allele frequency in gnomAD v4.1.0 for is 0.00004455 (2/44898 East Asian chromosomes), which is is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting. criterion also met if upper bound of the 95% CI for the European (non-Finnish) population used: 0.00003 (22/1179964).

Not Met criteria codes

PM5			Other amino acid changes at this position have been reported, but this code is not needed for a P classification and this variant seems to have the most evidence compared to the other missense changes.
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Curation History



 

 

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