

Variant: *NM_000070.3(CAPN3):c.1465C>T (p.Arg489Trp)*

Version: 1.0

CA347587 [↗](#)

217150 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 4c9f7d57-1a06-42f9-85a7-1b15a78d83fb

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HGVS expressions

NM_000070.3(CAPN3):c.1465C>T (p.Arg489Trp)

NM_000070.3:c.1465C>T

NC_000015.10:g.42401751C>T

CM000677.2:g.42401751C>T

NC_000015.9:g.42693949C>T

CM000677.1:g.42693949C>T

NC_000015.8:g.40481241C>T

NG_008660.1:g.58649C>T

ENST00000349748.8:c.1321C>T

ENST00000357568.8:c.1465C>T

ENST00000397163.8:c.1465C>T

ENST00000466369.5:n.1974C>T

ENST00000483208.5:n.1696C>T

ENST00000495723.1:n.1696C>T

ENST00000549793.5:n.1696C>T

ENST00000638141.2:n.1336C>T

ENST00000673705.1:c.309+2099C>T

ENST00000318023.11:c.1321C>T

ENST00000349748.7:c.1321C>T

ENST00000357568.7:c.1465C>T

ENST00000397163.7:c.1465C>T

NM_000070.2:c.1465C>T

NM_024344.1:c.1465C>T

NM_173087.1:c.1321C>T

NM_024344.2:c.1465C>T

NM_173087.2:c.1321C>T

Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM2_Supporting

PM3_Very Strong

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.1465C>T variant in CAPN3 is a missense variant expected to cause the substitution of arginine at amino acid position 489 with tryptophan, p.(Arg489Trp). Across a selection of the available literature, this variant has been identified in at least nine unrelated individuals with features of LGMD (PMID: 18055493, 27066573, 27708273, 37526466, 15689361; LOVD CAPN3_000038). In one patient, it was confirmed in trans with a pathogenic variant (c.1715G>A p.(Arg572Gln), 1.0 pt, PMID: 27708273), and in six patients, it was reported in unconfirmed phase with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 0.5 pts x4, PMID: 18055493, 37526466, 15689361; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts x2, PMID: 15689361) (PM3_Very Strong). At least one of these patients displayed progressive limb girdle muscle weakness (PP4). This variant has also been reported to segregate with autosomal recessive LGMD in one affected family member (PMID: 27708273; PP1). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000054578 (51/1179994 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold of 0.0001, meeting the criteria for PM2_Supporting. The computational predictor REVEL also gives a score of 0.752, which is above the threshold of 0.7, evidence that correlates with impact to CAPN3 function (PP3). 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; 04/29/2026): PM3_Very Strong, PP4, PP1, PM2_Supporting, PP3.

Met criteria codes

PP1			This variant has been reported to segregate with autosomal recessive LGMD in one affected family member (PMID: 27708273; PP1).
PP3			The computational predictor REVEL also gives a score of 0.752, which is above the threshold of 0.7, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.0100
PP4			At least one patient with this variant displayed progressive limb girdle muscle weakness (PP4).
PM2_Supporting			The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.000054578 (51/1179994 European (non-Finnish) alleles), which is lower than the LGMD VCEP threshold of 0.0001, meeting the criteria for PM2_Supporting.
PM3_Very Strong			Across a selection of the available literature, this variant has been identified in at least nine unrelated individuals with features of LGMD (PMID: 18055493, 27066573, 27708273, 37526466, 15689361; LOVD CAPN3_000038). In one patient, it was confirmed in trans with a pathogenic variant (c.1715G>A p.(Arg572Gln), 1.0 pt, PMID: 27708273), and in six patients, it was reported in unconfirmed phase with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 0.5 pts x4, PMID: 18055493, 37526466, 15689361; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts x2, PMID: 15689361) (PM3_Very Strong).

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