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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
Approved on: 2026/4/29
Published on: 2026/5/7

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

PM3_Very Strong | PM2_Supporting | PP1 | PP3 | PP4

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*

Criteria Specification Approval History
Criteria Specifications for this VCEP

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

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).
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.
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).

Curation History

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