

Variant: *NM_000070.3(CAPN3):c.1076C>T (p.Pro359Leu)*

Version: 1.0

CA247490 [↗](#)

198690 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 71dae65f-5eda-48c7-b87f-d1a68c7de555

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HGVS expressions

NM_000070.3:c.1076C>T

NM_000070.3(CAPN3):c.1076C>T (p.Pro359Leu)

NC_000015.10:g.42394302C>T

CM000677.2:g.42394302C>T

NC_000015.9:g.42686500C>T

CM000677.1:g.42686500C>T

NC_000015.8:g.40473792C>T

NG_008660.1:g.51200C>T

ENST00000349748.8:c.932C>T

ENST00000357568.8:c.1076C>T

ENST00000397163.8:c.1076C>T

ENST00000466369.5:n.1585C>T

ENST00000483208.5:n.1307C>T

ENST00000495723.1:n.1307C>T

ENST00000549793.5:n.1307C>T

ENST00000638141.2:n.947C>T

ENST00000673658.1:n.60C>T

ENST00000673705.1:c.71-2498C>T

ENST00000318023.11:c.932C>T

ENST00000349748.7:c.932C>T

ENST00000357568.7:c.1076C>T

ENST00000397163.7:c.1076C>T

NM_000070.2:c.1076C>T

NM_024344.1:c.1076C>T

NM_173087.1:c.932C>T

NM_024344.2:c.1076C>T

NM_173087.2:c.932C>T

Likely Pathogenic

Met criteria codes **4**

PM3

PP4_Strong

PP3

PM2_Supporting

Not Met criteria codes **1**

PM5

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.1076C>T variant in CAPN3 is a missense variant predicted to cause substitution of proline by leucine at amino acid 359 (p.Pro359Leu). This variant has been reported in at least 8 patients with clinical signs of LGMD, including in a homozygous state in at least 6 individuals (1.0 pt; PMID: 22926650, 17596655, 30564623; ClinVar SCV001524377.1, SCV001544778.3 internal data communication; LOVD CAPN3_000128) and in unconfirmed phase with a likely pathogenic variant in at least one individual (c.1256A>G p.(Asp419Gly), 0.25 pts, PMID: 30564623, LOVD Individual #00220445, GRASP-LGMD Consortium internal data communication) (PM3). At least one patient homozygous for this variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 17596655; PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.1 is 0.00001648 (1/60664 alleles) in the Remaining population, which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.955, which is above the 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; 04/28/2026): PM3, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM3			This variant has been reported in at least 8 patients with clinical signs of LGMD, including in a homozygous state in at least 6 individuals (1.0 pt; PMID: 22926650, 17596655, 30564623; ClinVar SCV001524377.1, SCV001544778.3 internal data communication; LOVD CAPN3_000128) and in unconfirmed phase with a likely pathogenic variant in at least one individual (c.1256A>G p.(Asp419Gly), 0.25 pts, PMID: 30564623, LOVD Individual #00220445, GRASP-LGMD Consortium internal data communication) (PM3). fails filter in gnomAD v2 exomes and not present in genomes so co-occurrence cannot be assessed
PP4_Strong			At least one patient homozygous for this variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 17596655; PP4_Strong).
PP3			The computational predictor REVEL gives a score of 0.955, which is above the threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.100
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.1 is 0.00001648 (1/60664 alleles) in the Remaining population, which is lower than the ClinGen LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5			No other variants at this codon in ClinVar.
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