The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2026/4/28
Published on: 2026/5/7

HGVS expressions

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

PP4_Strong PM2_Supporting PM3 PP3

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 Links 0

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.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

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).
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).
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
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

Not Met criteria codes

PM5	✖	No other variants at this codon in ClinVar.

Curation History

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