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.1099G>A (p.Gly367Ser)

Version: 1.0

CA7511243

468639 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: fc884768-c215-4a8e-8323-a607ace8ddb3
Approved on: 2025/10/28
Published on: 2025/11/11

HGVS expressions

NM_000070.3:c.1099G>A
NM_000070.3(CAPN3):c.1099G>A (p.Gly367Ser)
NC_000015.10:g.42394325G>A
CM000677.2:g.42394325G>A
NC_000015.9:g.42686523G>A
CM000677.1:g.42686523G>A
NC_000015.8:g.40473815G>A
NG_008660.1:g.51223G>A
ENST00000349748.8:c.955G>A
ENST00000357568.8:c.1099G>A
ENST00000397163.8:c.1099G>A
ENST00000466369.5:n.1608G>A
ENST00000483208.5:n.1330G>A
ENST00000495723.1:n.1330G>A
ENST00000549793.5:n.1330G>A
ENST00000638141.2:n.970G>A
ENST00000673658.1:n.83G>A
ENST00000673705.1:c.71-2475G>A
ENST00000318023.11:c.955G>A
ENST00000349748.7:c.955G>A
ENST00000357568.7:c.1099G>A
ENST00000397163.7:c.1099G>A
NM_000070.2:c.1099G>A
NM_024344.1:c.1099G>A
NM_173087.1:c.955G>A
NM_024344.2:c.1099G>A
NM_173087.2:c.955G>A

Likely Pathogenic

Met criteria codes 3

PP3 PP4 PM3_Strong

Not Met criteria codes 2

PM2 PM5

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.1099G>A variant in CAPN3 is a missense variant expected to result in the substitution of glycine with serine at amino acid 367, p.(Gly367Ser). This variant has been identified in at least 7 patients with features consistent with LGMD (PMID: 15689361, 17236769, 25079074, 32403337, 33250842, 34201303; ClinVar SCV000645461.5 internal data communication), including confirmed in trans with a whole gene deletion in one individual (1.0 pt, ClinVar SCV000645461.5 internal data communication) and in unconfirmed phase with a pathogenic variant in two cases (c.759_761del p.(Lys254del), 0.5 pts, PMID: 15689361; c.1322del p.(Gly441ValfsTer22), 0.5 pts, PMID: 34201303) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness (PP4). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003851 (the upper threshold of the 95% CI of 23/84620 South Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.955, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF 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 (LGMD VCEP specifications version 2.0.0; 10/28/2025): PP3, PM3_Strong, PP4.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.955, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to DYSF function (PP3). SpliceAI 0.01, not in a splice region.
PP4	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness (PP4). see citations for PM3
PM3_Strong	✔	This variant has been identified in at least 7 patients with features consistent with LGMD (PMID: 15689361, 17236769, 25079074, 32403337, 33250842, 34201303; ClinVar SCV000645461.5 internal data communication), including confirmed in trans with a whole gene deletion in one individual (1.0 pt, ClinVar SCV000645461.5 internal data communication) and in unconfirmed phase with a pathogenic variant in two cases (c.759_761del p.(Lys254del), 0.5 pts, PMID: 15689361; c.1322del p.(Gly441ValfsTer22), 0.5 pts, PMID: 34201303) (PM3_Strong). c.759_761del p.(Lys254del) is a proposed dominant variant but with weak segregation evidence c.1322del p.(Gly441ValfsTer22) and c.759_761del p.(Lys254del) are predicted on different haplotypes from the curated variant in gnomAD v2 discussed at 10/28/2025 VCEP call: agree to award pts for whole-gene deletion we can't enter into VCI directly because cannot generate CAID with uncertain breakends. Curating additional variants will not allow us to reach PM3_Very Strong c.224A>G p.Tyr75Cys (not in VCI, VUS in ClinVar), unknown phase c.1706T>C p. Phe569Ser (not in VCI, mixed in ClinVar), unknown phase

Not Met criteria codes

PM2	✖	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0003851 (the upper threshold of the 95% CI of 23/84620 South Asian chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met).

PM5		✖	no eligible variants to consider

Curation History

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