

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

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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**

PM3_Strong

PP3

PP4

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

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

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
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

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).
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PM5

no eligible variants to consider

Curation History [↗](#)

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