

Variant: *NM_000070.3(CAPN3):c.1322G>A (p.Gly441Asp)*

Version: 1.0

CA391999585 [↗](#)

2137655 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6ed54c3c-fa04-46be-9621-51dad94be0d1

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HGVS expressions

NM_000070.3(CAPN3):c.1322G>A (p.Gly441Asp)

NM_000070.3:c.1322G>A

NC_000015.10:g.42399620G>A

CM000677.2:g.42399620G>A

NC_000015.9:g.42691818G>A

CM000677.1:g.42691818G>A

NC_000015.8:g.40479110G>A

NG_008660.1:g.56518G>A

ENST00000349748.8:c.1178G>A

ENST00000357568.8:c.1322G>A

ENST00000397163.8:c.1322G>A

ENST00000466369.5:n.1831G>A

ENST00000483208.5:n.1553G>A

ENST00000495723.1:n.1553G>A

ENST00000549793.5:n.1553G>A

ENST00000638141.2:n.1193G>A

ENST00000673658.1:n.306G>A

ENST00000673705.1:c.277G>A

ENST00000318023.11:c.1178G>A

ENST00000349748.7:c.1178G>A

ENST00000357568.7:c.1322G>A

ENST00000397163.7:c.1322G>A

NM_000070.2:c.1322G>A

NM_024344.1:c.1322G>A

NM_173087.1:c.1178G>A

NM_024344.2:c.1322G>A

NM_173087.2:c.1178G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PP4_Strong

PP3

PM3

Not Met criteria codes 2

PP1

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.1322G>A variant in CAPN3 is a missense variant expected to result in the substitution of glycine with aspartic acid at amino acid 441, p.(Gly441Asp). This variant has been reported in four individuals with features consistent with LGMD (PMID: 16372320, 37526466, 16650086, 25135358; ClinVar SCV003442816.3 internal data communication), including in a homozygous state without reported familial consanguinity in one patient (0.5 pts; PMID: 16372320, 37526466, 25135358) and in unconfirmed phase with a pathogenic variant in two patients (c.550del p.(Thr184ArgfsTer36), 0.5 pts, ClinVar SCV003442816.3 internal data communication; c.1714C>T p.(Arg572Trp), 0.5 pts, PMID: 16650086) (PM3). At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and only trace amounts of calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 16650086). The variant is not found in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.916, 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; 10/29/2025): PM3, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting			The variant is not found in gnomAD v4.1.0 (PM2_Supporting).
PP4_Strong			At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and only trace amounts of calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 16650086). 35 year old female with LGMD symptoms since childhood. Western blot of muscle biopsy: 30 kDa 0 (absent), 60 kDa 0/— (trace), 94 kDa 0/— (trace). Unconfirmed phase with c.1714C>T (p.Arg572Trp), which is provisionally P;
PP3			The computational predictor REVEL gives a score of 0.916, 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
PM3			This variant has been reported in four individuals with features consistent with LGMD (PMID: 16372320, 37526466, 16650086, 25135358; ClinVar SCV003442816.3 internal data communication), including in a homozygous state without reported familial consanguinity in one patient (0.5 pts; PMID: 16372320, 37526466, 25135358) and in unconfirmed phase with a pathogenic variant in two patients (c.550del p.(Thr184ArgfsTer36), 0.5 pts, ClinVar SCV003442816.3 internal data communication; c.1714C>T p.(Arg572Trp), 0.5 pts, PMID: 16650086) (PM3). cannot asses co-occurrence predictions with variants in unconfirmed phase no other patients identified: In LOVD, Saenz et al. (2005) and Richard et al. (1999) each report a single hit. No other cases in LOVD. Fardeau et al. (1996) (PMID: 9027854) don't provide individual details and is a French study with potential overlap with Richard et al. and Krahn et al. Jia et al. (2003) (PMID: 11371436) is a modeling study that doesn't report any patients.

Not Met criteria codes

PP1		
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One of the patients with this variant was reported to have an affected sibling but phase was not confirmed (PMID: 16650086; PP1 not met).

PM5



no other missense variants at this position to consider

Curation History

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