

Variant: *NM_000070.3(CAPN3):c.1336G>A (p.Gly446Ser)*

Version: 1.0

CA10604779 [↗](#)

284385 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c5914cff-94c5-4f73-83bf-512bba9c7d62

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HGVS expressions

NM_000070.3(CAPN3):c.1336G>A (p.Gly446Ser)

NM_000070.3:c.1336G>A

NC_000015.10:g.42399634G>A

CM000677.2:g.42399634G>A

NC_000015.9:g.42691832G>A

CM000677.1:g.42691832G>A

NC_000015.8:g.40479124G>A

NG_008660.1:g.56532G>A

ENST00000349748.8:c.1192G>A

ENST00000357568.8:c.1336G>A

ENST00000397163.8:c.1336G>A

ENST00000466369.5:n.1845G>A

ENST00000483208.5:n.1567G>A

ENST00000495723.1:n.1567G>A

ENST00000549793.5:n.1567G>A

ENST00000638141.2:n.1207G>A

ENST00000673658.1:n.320G>A

ENST00000673705.1:c.291G>A

ENST00000318023.11:c.1192G>A

ENST00000349748.7:c.1192G>A

ENST00000357568.7:c.1336G>A

ENST00000397163.7:c.1336G>A

NM_000070.2:c.1336G>A

NM_024344.1:c.1336G>A

NM_173087.1:c.1192G>A

NM_024344.2:c.1336G>A

NM_173087.2:c.1192G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PP4_Moderate

PP3

PM3

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.1336G>A variant in CAPN3 is a missense variant predicted to cause the substitution of glycine by serine at amino acid position 446, p.(Gly446Ser). This variant has been identified in at least four patients with clinical signs of LGMD, including in a homozygous state (0.5 pts, PMID: 22443334) and confirmed in trans with a likely pathogenic or pathogenic variant (c.883_886delinsCTT p.(Asp295_Asn296delinsLeufsTer57), 1.0 pt, PMID: 30919934, LOVD Individual #00214368) (PM3). In the two other patients, a second presumed diagnostic CAPN3 variant was not identified (PMID: 18337726; GRASP-LGMD Consortium internal data communication). The patient homozygous for this variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 22443334; PP4_Moderate). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.99, which is above the LGMD VCEP 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_Moderate, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate			A patient homozygous for this variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 22443334; PP4_Moderate). LGMD with progressive muscle weakness, 15% control calpain-3 expression on WB.
PP3			The computational predictor REVEL gives a score of 0.99, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). spliceAI 0, not in a splice region
PM3			This variant has been identified in at least four patients with clinical signs of LGMD, including in a homozygous state (0.5 pts, PMID: 22443334) and confirmed in trans with a likely pathogenic or pathogenic variant (c.883_886delinsCTT p.(Asp295_Asn296delinsLeufsTer57), 1.0 pt, PMID: 30919934, LOVD Individual #00214368) (PM3). In the two other patients, a second presumed diagnostic CAPN3 variant was not identified (PMID: 18337726; GRASP-LGMD Consortium internal data communication). VUS by Labcorp, unknown affected status, suggesting they do not have internal cases

Not Met criteria codes

PM5			no other missense changes at this residue in ClinVar or LOVD.
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