

Variant: *NM_000070.3(CAPN3):c.1257T>G (p.Asp419Glu)*

Version: 1.0

CA7511304 [↗](#)

282873 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 607a2850-241c-440c-8f97-79c80a46e4c6

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HGVS expressions

NM_000070.3(CAPN3):c.1257T>G (p.Asp419Glu)

NM_000070.3:c.1257T>G

NC_000015.10:g.42399555T>G

CM000677.2:g.42399555T>G

NC_000015.9:g.42691753T>G

CM000677.1:g.42691753T>G

NC_000015.8:g.40479045T>G

NG_008660.1:g.56453T>G

ENST00000349748.8:c.1113T>G

ENST00000357568.8:c.1257T>G

ENST00000397163.8:c.1257T>G

ENST00000466369.5:n.1766T>G

ENST00000483208.5:n.1488T>G

ENST00000495723.1:n.1488T>G

ENST00000549793.5:n.1488T>G

ENST00000638141.2:n.1128T>G

ENST00000673658.1:n.241T>G

ENST00000673705.1:c.212T>G

ENST00000318023.11:c.1113T>G

ENST00000349748.7:c.1113T>G

ENST00000357568.7:c.1257T>G

ENST00000397163.7:c.1257T>G

NM_000070.2:c.1257T>G

NM_024344.1:c.1257T>G

NM_173087.1:c.1113T>G

NM_024344.2:c.1257T>G

NM_173087.2:c.1113T>G

Likely Pathogenic

Met criteria codes 4

PM3_Strong

PP3

PP4

PM2_Supporting

Not Met criteria codes 2

PS3

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.1257T>G variant in CAPN3 is a missense variant predicted to cause substitution of aspartic acid by glutamic acid at amino acid 419 (p.Asp419Glu). This variant has been detected in at least ten unrelated individuals with LGMD (PMID: 18055493, 25079074, 30564623; LOVD CAPN3_000280; ClinVar SCV000953543.3 internal data communication, ClinVar SCV002025057.3 internal data communication, ClinVar SCV001879783.1 internal data communication), including in unknown phase with a pathogenic variant in six cases (c.550delA p.(Thr184ArgfsTer36), 1.0 pt, PMID: 18055493, SCV002025057.3; c.1469G>A p.(Arg490Gln), 0.5 pts, ClinVar SCV000953543.3 internal data communication; c.1027G>T p.(Glu343Ter), 0.5 pts, ClinVar SCV000953543.3 internal data communication; c.1838del p.(Lys613ArgfsTer49), 0.5 pts, ClinVar SCV000953543.3 internal data communication; c.643_663del p.(Ser215_Gly221del), 0.5 pts, ClinVar SCV001879783.1 internal data communication) (PM3_Strong). In four individuals, a second variant in CAPN3 was not identified. At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PMID: 18055493) (PP4). The filtering allele frequency of this variant is 0.00006819 (the upper threshold of the 95% CI of 3/113704 European (non-Finnish) exome alleles) by gnomAD v2.1.1, which is less than the LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.83, which exceeds the 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 (LGMD VCEP specifications version 1.0.0; 01/09/2025): PM3_Strong, PP4, PM2_Supporting, PP3.

Met criteria codes

PM3_Strong			This variant has been detected in at least ten unrelated individuals with LGMD (PMID: 18055493, 25079074, 30564623; LOVD CAPN3_000280; Accession: SCV000953543.3, SCV002025057.3, SCV001879783.1), including in unknown phase with a pathogenic variant in six cases (c.550delA p.(Thr184ArgfsTer36), 1.0 pt, PMID: 18055493, SCV002025057.3; c.1469G>A p.(Arg490Gln), 0.5 pts, SCV000953543.3; c.1027G>T p.(Glu343Ter), 0.5 pts, SCV000953543.3; c.1838del p.(Lys613ArgfsTer49), 0.5 pts, SCV000953543.3; c.643_663del p.(Ser215_Gly221del), 0.5 pts, SCV001879783.1) (PM3_Strong).
PP3			The computational predictor REVEL gives a score of 0.83, which exceeds the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3).
PP4			At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PMID: 18055493) (PP4).
PM2_Supporting			The filtering allele frequency of this variant is 0.00006819 (the upper threshold of the 95% CI of 3/113704 European (non-Finnish) exome alleles) by gnomAD v2.1.1, which is less than the LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting).

Not Met criteria codes

PS3			A functional assay has suggested this variant increases the speed of calpain-3 autolysis compared to wild-type, resulting in premature enzyme inactivation (PMID: 19226146).
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PM5

c.1256A>G p.(Asp419Gly) VUS without PM5_Supporting

Curation History [↗](#)

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