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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
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

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

PP3 PP4 PM3_Strong PM2_Supporting

Not Met criteria codes 2

PM5 PS3

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 Links 0

Variant Interpretation Guidelines for CAPN3 Version 1.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.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

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).
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).
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

PM5	✖	c.1256A>G p.(Asp419Gly) VUS without PM5_Supporting

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).

Curation History

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