

Variant: *NM_000070.3(CAPN3):c.1256A>G (p.Asp419Gly)*

Version: 1.0

CA10604828 [↗](#)

284518 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e1096c5e-9eb9-40e7-87b5-1de5084d1a17

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HGVS expressions

NM_000070.3(CAPN3):c.1256A>G (p.Asp419Gly)

NM_000070.3:c.1256A>G

NC_000015.10:g.42399554A>G

CM000677.2:g.42399554A>G

NC_000015.9:g.42691752A>G

CM000677.1:g.42691752A>G

NC_000015.8:g.40479044A>G

NG_008660.1:g.56452A>G

ENST00000349748.8:c.1112A>G

ENST00000357568.8:c.1256A>G

ENST00000397163.8:c.1256A>G

ENST00000466369.5:n.1765A>G

ENST00000483208.5:n.1487A>G

ENST00000495723.1:n.1487A>G

ENST00000549793.5:n.1487A>G

ENST00000638141.2:n.1127A>G

ENST00000673658.1:n.240A>G

ENST00000673705.1:c.211A>G

ENST00000318023.11:c.1112A>G

ENST00000349748.7:c.1112A>G

ENST00000357568.7:c.1256A>G

ENST00000397163.7:c.1256A>G

NM_000070.2:c.1256A>G

NM_024344.1:c.1256A>G

NM_173087.1:c.1112A>G

NM_024344.2:c.1256A>G

NM_173087.2:c.1112A>G

Likely Pathogenic

Met criteria codes 5

PM3_Strong

PP3

PP4

PM5_Supporting

PM2_Supporting

Not Met criteria codes 21

BP5

BP7

BP4

BP3

BP1

BP2

PS1

PS2

PS3

PS4

PP1

PP2

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.1256A>G variant in CAPN3 is a missense variant predicted to cause substitution of aspartic acid by glycine at amino acid 419 (p.Asp419Gly). This variant has been detected in at least 5 individuals with limb girdle muscular dystrophy (PMID: 18055493, 30564623, ClinVar SCV003828989.2, Washington University internal clinic data communication), including in unknown phase with a pathogenic variant (c.643_663del p.(Ser215_Gly221del), 0.5 pts, PMID: 18055493; c.756_758del p.(Lys254del) x2, 1.0 pts, PMID: 30564623; Washington University internal clinic data communication) and confirmed in trans with a likely pathogenic or pathogenic variant (c.2440-1G>A, 1.0 pt, ClinVar SCV003828989.2 internal data communication) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4; PMID: 18055493). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008 (1/113712 exome alleles) in the European (non-Finnish) population, which is less than the LGMD VCEP threshold (≤ 0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.98, which exceeds the threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3). Another missense variant at the same codon, c.1257T>G p.(Asp419Glu), has been classified as likely pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5_Supporting). 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; 01/07/2025): PM3_Strong, PP4, PM2_Supporting, PP3, PM5_Supporting.

Met criteria codes

PM3_Strong	<div><div></div></div>	<div></div>	This variant has been detected in at least 5 individuals with limb girdle muscular dystrophy (PMID: 18055493, 30564623, SCV003828989.2, Washington University clinic data), including in unknown phase with a pathogenic variant (c.643_663del p.(Ser215_Gly221del), 0.5 pts, PMID: 18055493; c.756_758del p.(Lys254del), 1.0 pts, PMID: 30564623; Washington University clinic data) and confirmed in trans with a likely pathogenic or pathogenic variant (c.2440-1G>A, 1.0 pt, SCV003828989.2) (PM3_Strong).
PP3	<div><div></div></div>	<div></div>	The computational predictor REVEL gives a score of 0.98, which exceeds the threshold of ≥ 0.70 , evidence that correlates with impact to DYSF function (PP3).
PP4	<div><div></div></div>	<div></div>	At least one patient with this variant displayed progressive weakness, which is specific for LGMD 2A (PP4_Supporting, PMID: 18055493).
PM5_Supporting	<div><div></div></div>	<div></div>	Another missense variant at the same codon, c.1257T>G p.(Asp419Glu), has been classified as Likely Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5_Supporting).
PM2_Supporting	<div><div></div></div>	<div></div>	The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008 (1/113712 exome alleles) in the European (non-Finnish) population, which is less than the LGMD VCEP threshold (≤ 0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting)

Not Met criteria codes

BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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