

Variant: *NM_000070.3(CAPN3):c.1303G>A (p.Glu435Lys)*

Version: 1.0

CA7511313 [↗](#)

282173 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a66ea791-1c1a-4480-a3a9-9a45118fc74e

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HGVS expressions

NM_000070.3:c.1303G>A

NM_000070.3(CAPN3):c.1303G>A (p.Glu435Lys)

NC_000015.10:g.42399601G>A

CM000677.2:g.42399601G>A

NC_000015.9:g.42691799G>A

CM000677.1:g.42691799G>A

NC_000015.8:g.40479091G>A

NG_008660.1:g.56499G>A

ENST00000349748.8:c.1159G>A

ENST00000357568.8:c.1303G>A

ENST00000397163.8:c.1303G>A

ENST00000466369.5:n.1812G>A

ENST00000483208.5:n.1534G>A

ENST00000495723.1:n.1534G>A

ENST00000549793.5:n.1534G>A

ENST00000638141.2:n.1174G>A

ENST00000673658.1:n.287G>A

ENST00000673705.1:c.258G>A

ENST00000318023.11:c.1159G>A

ENST00000349748.7:c.1159G>A

ENST00000357568.7:c.1303G>A

ENST00000397163.7:c.1303G>A

NM_000070.2:c.1303G>A

NM_024344.1:c.1303G>A

NM_173087.1:c.1159G>A

NM_024344.2:c.1303G>A

NM_173087.2:c.1159G>A

Pathogenic

Met criteria codes **3**

PM3_Very Strong

PP3

PP4_Strong

Not Met criteria codes **2**

PM2

PS1

Evidence Links **0**

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.1303G>A variant in CAPN3 is a missense variant expected to result in the substitution of glutamine for lysine at amino acid 435, p.(Glu435Lys). This variant has been detected in at least 8 individuals with features of LGMD (PMID: 20635405, 35157181, 18854869, 38812636, 33931068, 30564623; LOVD CAPN3_000134), including in a homozygous state in two unrelated patients without reported familial consanguinity (0.5 pts x2 = 1.0 pt, PMID: 35157181, 30564623, LOVD Individual #00222544). In addition, the variant was confirmed in trans with a likely pathogenic or pathogenic variant in at least three individuals (c.598_612del (p.Phe200_Leu204del), 1.0 pt, PMID: 33931068; c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 38812636; c.967G>T p.(Glu323Ter), 1.0 pt, PMID: 18854869) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 18854869) (PP4_Strong). The highest population minor allele frequency of this variant is 0.0003357 (15/44684 exome chromosomes) for the Admixed American population in gnomAD v4.1.0), which is higher than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). The computational predictor REVEL gives a score of 0.815, 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 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; 05/14/2025): PM3_Very Strong, PP4_Strong, PP3.

Met criteria codes

PM3_Very Strong			This variant has been detected in at least 8 individuals with features of LGMD (PMID: 20635405, 35157181, 18854869, 38812636, 33931068, 30564623; LOVD CAPN3_000134), including in a homozygous state in two unrelated patients without reported familial consanguinity (0.5 pts x2 = 1.0 pt, PMID: 35157181, 30564623, LOVD Individual #00222544). In addition, the variant was confirmed in trans with a likely pathogenic or pathogenic variant in at least three individuals (c.598_612del (p.Phe200_Leu204del), 1.0 pt, PMID: 33931068; c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 38812636; c.967G>T p.(Glu323Ter), 1.0 pt, PMID: 18854869) (PM3_Very Strong).
PP3			The computational predictor REVEL gives a score of 0.815, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function.
PP4_Strong			At least one patient with this variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 18854869) (PP4_Strong). PMID: 18854869: patient with progressive weakness and no detectable Calpain protein on WB. c.967G>T (p.Glu323Ter) (P) in trans

Not Met criteria codes

PM2			The highest minor allele frequency of this variant is 0.0003357 (15/44684 exome chromosomes) for the Admixed American population in gnomAD v4.1.0), which is higher than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).
PS1			

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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