

Variant: NM_000070.3(CAPN3):c.1622G>A (p.Arg541Gln)

Version: 2.0

CA220342 [↗](#)

92407 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: 9a15c9b5-3d55-403b-99ce-f3ec5b0adfc3
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HGVS expressions

NM_000070.3(CAPN3):c.1622G>A (p.Arg541Gln)
NM_000070.3:c.1622G>A
NC_000015.10:g.42402879G>A
CM000677.2:g.42402879G>A
NC_000015.9:g.42695077G>A
CM000677.1:g.42695077G>A
NC_000015.8:g.40482369G>A
NG_008660.1:g.59777G>A
ENST00000349748.8:c.1478G>A
ENST00000357568.8:c.1622G>A
ENST00000397163.8:c.1622G>A
ENST00000466369.5:n.2131G>A
ENST00000483208.5:n.2511G>A
ENST00000495723.1:n.2511G>A
ENST00000549793.5:n.1853G>A
ENST00000638141.2:n.1493G>A
ENST00000673646.1:c.86G>A
ENST00000673705.1:c.309+3227G>A
ENST00000673813.1:n.544G>A
ENST00000318023.11:c.1478G>A
ENST00000349748.7:c.1478G>A
ENST00000357568.7:c.1622G>A
ENST00000397163.7:c.1622G>A
ENST00000397200.8:c.86G>A
ENST00000567071.5:c.81G>A
ENST00000569827.5:c.86G>A
NM_000070.2:c.1622G>A
NM_024344.1:c.1622G>A
NM_173087.1:c.1478G>A
NM_173088.1:c.86G>A
NM_024344.2:c.1622G>A
NM_173087.2:c.1478G>A
NM_173088.2:c.86G>A

Pathogenic

PM3_Very Strong

PP3

PP4

PM2_Supporting

Not Met criteria codes 2

PM5

PVS1

Evidence Links 0

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Criteria Specification: ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CAPN3 Version 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel		
Limb Girdle Muscular Dystrophy VCEP The NM_000070.3: c.1622G>A variant in CAPN3 is a missense variant predicted to cause the substitution of arginine at amino acid position 541 with glutamine, p.(Arg541Gln). This variant has been identified in at least 18 individuals with features consistent with LGMD (PMID: 10330340, 1641109, 32994280, 30564623, 16141003, 30919934; LOVD CAPN3_000024; GRASP-LGMD Consortium internal data communication; ClinVar SCV001164515.1), including in a homozygous state without reported consanguinity in three unrelated patients (1.0 pt, PMID: 10330340, 30919934). It has also been reported in unconfirmed phase with a pathogenic variant in at least six patients (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 32994280, LOVD Individual #00311302; c.1469G>A p.(Arg490Gln), 0.5 pts, PMID: 16141003, LOVD Individual #00214226; c.550del p.(Thr184ArgfsTer36) x4, 2.0 pts, PMID: 16141003, LOVD Individuals #00214228, #00214229, GRASP-LGMD Consortium internal data communication; ClinVar SCV001164515.1 internal data communication) (PM3_Very Strong). At least one patient with this variant and another presumed diagnostic CAPN3 variant exhibited progressive limb girdle muscle weakness (PMID: 1614100; PP4). The highest population variant allele frequency in gnomAD v4.1.0 is 0.00002196 (2/91082 South Asian chromosomes), which is lower than the VCEP threshold of 0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.908, which is above the VCEP threshold of ≥ 0.70, evidence that correlates with impact to CAPN3 function (PP3). A minigene assay showed altered splicing in a minority of transcripts but without a significant reduction in normally spliced transcript (PMID: 32668095; PVS1_RNA not met). The SpliceAI score is 0.02. In summary, this variant meets criteria to be classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy based on the ACMG criteria applied, as specified by the LGMD VCEP (specifications version 2.0.0, 02/18/2026): PM3_Very Strong, PP4, PM2_Supporting, PP3.		
Met criteria codes		
PM3_Very Strong	i ✓	This variant has been identified in at least 18 individuals with features consistent with LGMD (PMID: 10330340, 1641109, 32994280, 30564623, 16141003, 30919934; LOVD CAPN3_000024; GRASP-LGMD Consortium internal data communication; ClinVar SCV001164515.1), including in a homozygous state without reported consanguinity in three unrelated patients (1.0 pt, PMID: 10330340, 30919934). It has also been reported in unconfirmed phase with a pathogenic variant in at least six patients (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 32994280, LOVD Individual #00311302; c.1469G>A p.(Arg490Gln), 0.5 pts, PMID: 16141003, LOVD Individual #00214226; c.550del p.(Thr184ArgfsTer36) x4, 2.0 pts, PMID: 16141003, LOVD Individuals #00214228, #00214229, GRASP-LGMD Consortium internal data communication; ClinVar SCV001164515.1 internal data communication) (PM3_Very Strong). unconfirmed phase: c.550del p.(Thr184ArgfsTer36) x4: predicted on different haplotypes c.2120A>G p.(Asp707Gly): predicted on different haplotypes c.1469G>A p.(Arg490Gln): predicted on different haplotypes unscored cases unconfirmed phase with c.2148G>T p.(Glu716Asp) unconfirmed phase with c.767T>C p.(Ile256Thr) unconfirmed phase with c.2185-5_2190dup unconfirmed phase with c.1073A>G p.(Asn358Ser) unconfirmed phase with c.822T>G p.(Tyr274Ter) unconfirmed phase with c.802-9G>A x2 unconfirmed phase with c.755T>A p.(Met252Lys)
PP3	i ✓	The computational predictor REVEL gives a score of 0.908, which is above the VCEP threshold of ≥ 0.70, evidence that correlates with impact to CAPN3 function (PP3). spliceAI 0.02

PP4			At least one patient with this variant and another presumed diagnostic CAPN3 variant exhibited progressive limb girdle muscle weakness (PMID: 1614100; PP4).
PM2_Supporting			The highest population variant allele frequency in gnomAD v4.1.0 is 0.00002196 (2/91082 South Asian chromosomes), which is lower than the VCEP threshold of 0.0001 (PM2_Supporting). Criterion also met using the upper bound of the 95% confidence interval for the European (non-Finnish) population
Not Met criteria codes			
PM5			Another amino acid change at the same position, c.1621C>T p.(Arg541Trp), is classified as Pathogenic without use of PM5: PM3_Very Strong, PP4, PP1_Moderate, PM2_Supporting, PP3. Both have REVEL scores >0.7 and spliceAI scores <0.05, so the code requirements are met. However, the Grantham difference for Arg-Trp (101) is significantly higher than than for Arg-Gln (43). Since a P classification for p.(Arg541Gln) already met, code not applied.
PVS1			A minigene assay showed altered splicing in a minority of transcripts but without a significant reduction in normally spliced transcript (PMID: 32668095; PVS1_RNA not met).

Curation History 	
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