

Variant: NM_000070.3(CAPN3):c.2306G>A (p.Arg769Gln)

Version: 1.0

CA127306 [↗](#)

17613 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: f1a2c1a0-76fc-4e97-873f-3b47fb3f5aaf
Approved on: 2025/4/22
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HGVS expressions

NM_000070.3(CAPN3):c.2306G>A (p.Arg769Gln)
NM_000070.3:c.2306G>A
NC_000015.10:g.42410926G>A
CM000677.2:g.42410926G>A
NC_000015.9:g.42703124G>A
CM000677.1:g.42703124G>A
NC_000015.8:g.40490416G>A
NG_008660.1:g.67824G>A
ENST00000337571.9:c.311G>A
ENST00000349748.8:c.2030G>A
ENST00000357568.8:c.2288G>A
ENST00000397163.8:c.2306G>A
ENST00000397204.9:c.311G>A
ENST00000466222.7:n.751G>A
ENST00000466369.5:n.2797G>A
ENST00000495723.1:n.3177G>A
ENST00000549793.5:n.2519G>A
ENST00000562199.2:c.310G>A
ENST00000567817.6:c.95G>A
ENST00000568153.2:c.172G>A
ENST00000569136.6:c.311G>A
ENST00000638141.2:n.2045G>A
ENST00000673646.1:c.870G>A
ENST00000673684.1:n.288G>A
ENST00000673692.1:c.311G>A
ENST00000673705.1:c.849G>A
ENST00000673743.1:c.209G>A
ENST00000673750.1:c.311G>A
ENST00000673771.1:c.311G>A
ENST00000673774.1:n.1439G>A
ENST00000673839.1:c.311G>A
ENST00000673851.1:c.311G>A
ENST00000673854.1:n.5728G>A
ENST00000673886.1:c.311G>A
ENST00000673890.1:c.311G>A
ENST00000673928.1:c.311G>A
ENST00000673936.1:c.311G>A

	ENST00000673939.1:c.*100G>A ENST00000673950.1:n.580G>A ENST00000673978.1:c.449G>A ENST00000673987.1:c.*100G>A ENST00000674011.1:c.*100G>A ENST00000674018.1:c.311G>A ENST00000674027.1:n.457G>A ENST00000674041.1:c.311G>A ENST00000674052.1:c.530G>A ENST00000674093.1:c.311G>A ENST00000674119.1:c.311G>A ENST00000674135.1:c.488G>A ENST00000674139.1:c.311G>A ENST00000674146.1:c.311G>A ENST00000674149.1:c.311G>A ENST00000318023.11:c.2162G>A ENST00000337571.8:c.311G>A ENST00000349748.7:c.2030G>A ENST00000356316.7:c.311G>A ENST00000357568.7:c.2288G>A ENST00000397163.7:c.2306G>A ENST00000397200.8:c.770G>A ENST00000397204.8:c.311G>A ENST00000466222.6:n.1229G>A ENST00000561817.5:c.311G>A ENST00000562199.1:n.310G>A ENST00000564503.5:c.349G>A ENST00000565274.5:c.484G>A ENST00000567817.5:c.122G>A ENST00000568153.1:c.43G>A ENST00000569136.5:c.311G>A ENST00000569827.5:c.638G>A NM_000070.2:c.2306G>A NM_024344.1:c.2288G>A NM_173087.1:c.2030G>A NM_173088.1:c.770G>A NM_173089.1:c.311G>A NM_173090.1:c.311G>A NM_024344.2:c.2288G>A NM_173087.2:c.2030G>A NM_173088.2:c.770G>A NM_173089.2:c.311G>A NM_173090.2:c.311G>A
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Pathogenic

Met criteria codes 5

- PP1_Strong
- PM2_Supporting
- PP3
- PP4
- PM3

Not Met criteria codes 4

- PVS1
- BP7
- 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.2306G>A variant in CAPN3 is a missense variant predicted to cause the substitution of arginine by glutamine at amino acid position 769, p.(Arg769Gln). The variant has been detected in a homozygous state in more than 30 individuals with LGMD (1.0 pt, PMID: 14645990, 12461690, 7720071, 23553538, LOVD CAPN3_000013; PM3). It was also observed to segregate with autosomal recessive LGMD in eight affected family members from two families and was found in a homozygous state in all affected patients in 10 families from the Plain community in northern Indiana (PMID: 12461690, 7720071; PP1_Strong). At least one patient homozygous for this variant showed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 14645990; PP4 (capped with PP1_Strong)). The filtering allele frequency of this variant is 0.000089887 in gnomAD v4.1.0 exomes (the upper threshold of the 95% CI of 3/86258 South Asian chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.947, which is above the threshold of 0.70 (PP3). SpliceAI predicts the possible loss of an alternate splice donor site due to this variant, with a score of 0.49. However, a minigene assay for this variant demonstrated a largely preserved expression of transcripts with normal splicing (PMID: 32668095). In summary, this variant is classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the ClinGen LGMD VCEP (LGMD VCEP specifications version 1.0.0; 04/22/2025). While the ACMG/AMP criteria applied, as specified by the ClinGen LGMD VCEP, result in 9 Bayesian points (PM3, PP1_Strong, PP4, PM2_Supporting, PP3), a classification of Pathogenic was awarded given the strength of the available evidence and the impact of scoring caps on homozygous case data and locus-specific segregation and phenotype evidence.

Met criteria codes

PP1_Strong			This variant was observed to segregate with autosomal recessive LGMD in 8 affected family members from two families and was found in a homozygous state in all affected patients in 10 families from the Plain community in northern Indiana (PMID: 12461690, 7720071; PP1_Strong).
PM2_Supporting			The filtering allele frequency of this variant is 0.000089887 (the upper threshold of the 95% CI of 3/86258 South Asian exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤ 0.0001) (PM2_Supporting).
PP3			The computational predictor Revel gives a score of 0.947, which is above the threshold of 0.70 (PP3). SpliceAI score of 0.49 for donor loss, but minigene assay suggest splice impact negligible, if any.
PP4			At least one patient homozygous for this variant showed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 14645990; PP4 (capped with PP1_Strong)).
PM3			The variant has been detected in a homozygous state in more than 30 individuals with LGMD (1.0 pt, PMID: 14645990, 12461690, 7720071, 23553538, LOVD CAPN3_000013; PM3). ~34 total homozygous cases in LOVD, especially from Nallamilli et al.; these cannot be awarded points given the cap on homozygosity at 1 pt.

Not Met criteria codes

PVS1			Minigene assay suggested a possible mild impact on splicing (possible loss of a minor non-canonical natural splice form with a shortened exon 22 containing only the first 43 nt), but a largely preserved expression of transcripts with normal splicing (PMID: 32668095; PVS1_RNA not met). SpliceAI gives a donor loss of 0.49 at the location of this variant, which is 1/3 of the way into exon 22. VCEP consensus that the possible mild splice effect suggested on minigene assay looks non-significant. High Revel score (0.94), PP3 currently applied. If we consider minigene assay as evidence of no splice impact, BP7_Strong_RNA would not apply because cannot exclude protein impact.
BP7			Even if we consider minigene assay as evidence of no splice impact, BP7_Strong_RNA would not apply because cannot exclude protein impact with high REVEL score.
PS3			In an in vitro assay, cells expressing this variant showed severely reduced calpain-3 protein expression on Western blot, indicating that this variant impacts protein function (PMID: 9642272). No approved functional assays for calpain-3 (PS3 not met).
PM5			c.2306G>C (p.Arg769Pro) preliminarily curated (currently VUS). Both c.2306G>C and G>A have SpliceAI scores above the threshold of 0.1, so PM5 cannot be considered under current specification guidelines, even if we consider mini-gene assay as evidence of normal splicing for G>A.

Curation History 	
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