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Variant: NM_000070.3(CAPN3):c.2306G>C (p.Arg769Pro)

Version: 1.0

CA392002041

652571 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1370b0a2-bea2-462c-8438-b3b9d0ce5615
Approved on: 2026/3/12
Published on: 2026/4/9

HGVS expressions

NM_000070.3:c.2306G>C
NM_000070.3(CAPN3):c.2306G>C (p.Arg769Pro)
NC_000015.10:g.42410926G>C
CM000677.2:g.42410926G>C
NC_000015.9:g.42703124G>C
CM000677.1:g.42703124G>C
NC_000015.8:g.40490416G>C
NG_008660.1:g.67824G>C
ENST00000337571.9:c.311G>C
ENST00000349748.8:c.2030G>C
ENST00000357568.8:c.2288G>C
ENST00000397163.8:c.2306G>C
ENST00000397204.9:c.311G>C
ENST00000466222.7:n.751G>C
ENST00000466369.5:n.2797G>C
ENST00000495723.1:n.3177G>C
ENST00000549793.5:n.2519G>C
ENST00000562199.2:c.310G>C
ENST00000567817.6:c.95G>C
ENST00000568153.2:c.172G>C
ENST00000569136.6:c.311G>C
ENST00000638141.2:n.2045G>C
ENST00000673646.1:c.870G>C
ENST00000673684.1:n.288G>C
ENST00000673692.1:c.311G>C
ENST00000673705.1:c.849G>C
ENST00000673743.1:c.209G>C
ENST00000673750.1:c.311G>C
ENST00000673771.1:c.311G>C
ENST00000673774.1:n.1439G>C
ENST00000673839.1:c.311G>C
ENST00000673851.1:c.311G>C
ENST00000673854.1:n.5728G>C
ENST00000673886.1:c.311G>C
ENST00000673890.1:c.311G>C
ENST00000673928.1:c.311G>C
ENST00000673936.1:c.311G>C

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

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM5 PM2_Supporting

Not Met criteria codes 1

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 1

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.2306G>C variant in CAPN3 is a missense variant predicted to cause the substitution of arginine by proline at amino acid position 769, p.(Arg769Pro). It has been detected in at least 7 unrelated patients with features consistent with LGMD (PMID: 25987458, 32994280, 37974208, 16607617; ClinVar SCV000948242.5 internal data communication), including in a homozygous state without reported consanguinity in one case (0.5 pts, PMID: 37974208) and confirmed in trans with a pathogenic variant in one case (c.2120A>G (p.Asp707Gly), 1.0 pt, PMID: 37974208) (PM3). At least one individual with this variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 37974208; PP4). The highest population frequency of this variant is 0.00001666 in the Admixed American population of gnomAD v4.1.0 (1/60020 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.956, which is above the threshold of 0.70 (PP3). In addition, another missense change at the same position, c.2306G>A p.(Arg769Gln), has been classified as pathogenic for autosomal recessive LGMD by the LGMD VCEP (PM5). 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 2.0.0; 03/12/2026): PM3, PP4, PM2_Supporting, PP3, PM5.

Met criteria codes

PP3	✓	The computational predictor Revel gives a score of 0.956, which is above the threshold of 0.70 (PP3).
PP4	✓	At least one individual with this variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD. PMID: 37974208
PM3	✓	The variant has been detected in at least 7 unrelated patients with features consistent with LGMD (PMID: 25987458, 32994280, 37974208, 16607617; ClinVar SCV000948242.5 internal data communication), including in a homozygous state without reported consanguinity in one case (0.5 pts, PMID: 37974208) and confirmed in trans with a pathogenic variant in one case (c.2120A>G (p.Asp707Gly), 1.0 pt, PMID: 37974208) (PM3). PM3_Very Strong (4 pts) needed to go from LP to P; currently at 1.5 PM3 pts so need 2.5 unscored cases: c.2050+1G>A: unknown phase, 0.5 if P; exon 18 skipping would be out of frame, cryptic use would be out of frame; expect PVS1; preliminary curation suggests P (in VCI) c.1343G>T p.(Arg448Leu): unknown phase, 0.5 if P; ; preliminary curation suggests LP (in VCI) c.802-9G>A: unknown phase, 0.5 if P; PP3 applies; preliminary curation suggests P (in VCI) c.1720T>G p.(Phe574Val): in trans, 1.0 if LP; preliminary curation suggests VUS since only a single patient (in VCI) no additional curation pursued at this time
PM5	✓	Another missense change at the same position, c.2306G>A p.(Arg769Gln), has been classified as pathogenic for autosomal recessive LGMD by the LGMD VCEP (PM5). requirements: The Revel score for curated variant is >0.7 Not located near an exon-intron boundary. The highest unmasked SpliceAI score for the curated variant is 0.01 (<0.5 threshold). (The masked 0.51 score is for weakening a cryptic donor, which we consider unlikely to be clinically significant.) The highest unmasked SpliceAI score for the comparison variant is 0.02 (<0.5 threshold). (The masked 0.49 score is for weakening a cryptic donor, which we consider unlikely to be clinically significant.) The comparison variant has been approved at Pathogenic independent of the classification of this variant. delta Ref Alt Acceptor Loss 0.05 -131 bp 0.58 0.53 Donor Loss 0.51 0 bp 0.54 0.04 Acceptor Gain 0.01 9 bp 0.00 0.01 Donor Gain 0.00 69 bp 0.01 0.0

PM2_Supporting ✔

The highest population allele frequency of this variant is 0.00001666 in the Admixed American population of gnomAD v4.1.0 (1/60020 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Not Met criteria codes

PS3 ✖

In vitro assays in COS7 cells demonstrated this variant causes hyper-rapid autolysis but absent substrate proteolysis (PMID: 26363099, 9642272), but this is not an approved assay for PS3.

1. signs of myopathy or dystrophy are present in skeletal muscle 2. an effect on gene or protein function is demonstrated (e.g., decreased protein expression, impaired membrane localization, or other functional abnormality) These two articles discusses the R769Q mutation in cell cultures, but does not present new experimental data from human muscle tissue specifically for this variant. However, it summarizes prior findings (including their own earlier studies) indicating that R769Q causes hyper-rapid autolysis, leading to absent CAPN3 protein in Western blot from muscle. PMID 26363099, 9642272 (Ono 1998, 2016) COS7 cells – a monkey kidney fibroblast cell line. Transfected with human p94 (CAPN3) wild-type or mutant cDNA. Western blot performed on: Total COS7 cell lysates (not muscle). antibodies used: Anti-IS2: Targets the IS2 domain unique to p94 (CAPN3). Anti-fodrin cleavage product: To detect 150-kDa fragment indicating proteolytic activity. Key observations: WT CAPN3 showed a 55-kDa autolytic fragment. R769Q was not detected, unless co-expressed with the C129S inactive mutant (indicating hyper-rapid autolysis). All mutants (including R769Q) failed to generate the 150-kDa fodrin cleavage fragment → no substrate proteolysis. PubMed:26363099

Curation History

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