The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000070.3(CAPN3):c.1343G>A (p.Arg448His)

Version: 1.0

CA347482

217149 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: c8bd6484-ecbf-4b5a-bc87-a052f79f612e
Approved on: 2026/1/20
Published on: 2026/2/17

HGVS expressions

NM_000070.3:c.1343G>A
NM_000070.3(CAPN3):c.1343G>A (p.Arg448His)
NC_000015.10:g.42399641G>A
CM000677.2:g.42399641G>A
NC_000015.9:g.42691839G>A
CM000677.1:g.42691839G>A
NC_000015.8:g.40479131G>A
NG_008660.1:g.56539G>A
ENST00000349748.8:c.1199G>A
ENST00000357568.8:c.1343G>A
ENST00000397163.8:c.1343G>A
ENST00000466369.5:n.1852G>A
ENST00000483208.5:n.1574G>A
ENST00000495723.1:n.1574G>A
ENST00000549793.5:n.1574G>A
ENST00000638141.2:n.1214G>A
ENST00000673658.1:n.327G>A
ENST00000673705.1:c.298G>A
ENST00000318023.11:c.1199G>A
ENST00000349748.7:c.1199G>A
ENST00000357568.7:c.1343G>A
ENST00000397163.7:c.1343G>A
NM_000070.2:c.1343G>A
NM_024344.1:c.1343G>A
NM_173087.1:c.1199G>A
NM_024344.2:c.1343G>A
NM_173087.2:c.1199G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4_Strong PM3_Strong

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*

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.1343G>A variant in CAPN3 is a missense variant expected to result in the substitution of arginine with histidine at amino acid 448, p.(Arg448His). This variant has been reported in at least 19 unrelated patients with features consistent with limb-girdle muscular dystrophy (PMID: 18854869, 9150160, 32994280, 30564623, 30919934, 25135358, 27447704, 16141003; LOVD CAPN3_000096). It has been observed in the homozygous state in one patient without reported consanguinity (0.5 pts; PMID: 30919934; LOVD Individual #00313874) as well as in five Indian patients without known relatedness but possible consanguinity (0.5 pts; PMID: 35169782). It has also been identified in a heterozygous state in unconfirmed phase with a pathogenic or likely pathogenic CAPN3 variant in several patients, including c.550del (0.5 pts; PMID: 18854869), c.1319G>A p.(Arg440Gln) (0.25 pts; PMID: 18854869), c.2362_2363delinsTCATCT p.(Arg788SerfsTer14) (0.5 pts; PMID: 9150160), and c.2120A>G p.(Asp707Gly) (0.5 pts; PMID: 32994280) (PM3_Strong). At least one patient with two presumed diagnostic CAPN3 alleles, including 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 allele frequency of this variant is 0.000002630 in the Admixed American population of gnomAD v4.1.0 (1/58530 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). The computational predictor REVEL gives a score of 0.904, 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 2.0.0; 01/20/2026): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✔	The highest population allele frequency of this variant is 0.000002630 in the Admixed American population of gnomAD v4.1.0 (1/58530 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting). Grpmax Filtering AF: European (non-Finnish) 95% confidence: 0.000011208, also meets PM2_Supporting
PP3	✔	The computational predictor REVEL gives a score of 0.904, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.00
PP4_Strong	✔	At least one patient with two presumed diagnostic CAPN3 alleles, including 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).
PM3_Strong	✔	The c.1343G>A (p.Arg448His) variant has been reported in at least 19 unrelated patients with features consistent with limb-girdle muscular dystrophy (PMID: 18854869, 9150160, 32994280, 30564623, 30919934, 25135358, 27447704, 16141003; LOVD CAPN3_000096). It has been observed in the homozygous state in one patient without reported consanguinity (0.5 pts; PMID: 30919934; LOVD Individual #00313874) as well as in five Indian patients without known relatedness but possible consanguinity (0.5 pts; PMID: 35169782). It has also been identified in a heterozygous state in unconfirmed phase with a pathogenic or likely pathogenic CAPN3 variant in several patients, including c.550del (0.5 pts; PMID: 18854869), c.1319G>A p.(Arg440Gln) (0.25 pts; PMID: 18854869), c.2362_2363delinsTCATCT p.(Arg788SerfsTer14) (0.5 pts; PMID: 9150160), and c.2120A>G p.(Asp707Gly) (0.5 pts; PMID: 32994280) (PM3_Strong). co-occurrence for scored variants in unconfirmed phase: c.550del p.(Thr184ArgfsTer36): predicted on different haplotypes c.1319G>A (p.Arg440Gln): predicted on different haplotypes

c.2362_2363delinsTCATCT (p.Arg788SerfsTer14): not in gnomAD v2 c.2120A>G (p.Asp707Gly): predicted on different haplotypes Co-occurrences with variants of uncertain or unestablished pathogenicity (c.1992+1G>T, c.2393C>A (p.Ala798Glu), c.2371G>A (p.Gly791Ser), c.1657G>A (p.Glu553Lys), c.2093G>A (p.Arg698His), c.1043del (p.Gly348fs), c.2442G>C (p.Trp814Cys)) were not scored.

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.