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>T (p.Arg448Leu)

Version: 1.0

CA391999624

1180840 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: b708dc64-c8c3-4823-a58b-ad4406c82733
Approved on: 2026/3/12
Published on: 2026/4/9

HGVS expressions

NM_000070.3:c.1343G>T
NM_000070.3(CAPN3):c.1343G>T (p.Arg448Leu)
NC_000015.10:g.42399641G>T
CM000677.2:g.42399641G>T
NC_000015.9:g.42691839G>T
CM000677.1:g.42691839G>T
NC_000015.8:g.40479131G>T
NG_008660.1:g.56539G>T
ENST00000349748.8:c.1199G>T
ENST00000357568.8:c.1343G>T
ENST00000397163.8:c.1343G>T
ENST00000466369.5:n.1852G>T
ENST00000483208.5:n.1574G>T
ENST00000495723.1:n.1574G>T
ENST00000549793.5:n.1574G>T
ENST00000638141.2:n.1214G>T
ENST00000673658.1:n.327G>T
ENST00000673705.1:c.298G>T
ENST00000318023.11:c.1199G>T
ENST00000349748.7:c.1199G>T
ENST00000357568.7:c.1343G>T
ENST00000397163.7:c.1343G>T
NM_000070.2:c.1343G>T
NM_024344.1:c.1343G>T
NM_173087.1:c.1199G>T
NM_024344.2:c.1343G>T
NM_173087.2:c.1199G>T

Likely Pathogenic

Met criteria codes 5

PM5 PP3 PP4 PM3_Strong PM2_Supporting

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>T variant in CAPN3 is a missense variant predicted to cause the substitution of arginine by leucine at amino acid position 448, p.(Arg448Leu). This variant has been identified in at least six unrelated individuals with features consistent with LGMD (PMID: 25987458, 29797799, 22926650, 33250842, 32994280, 28403181), including in a homozygous state in one patient without reported consanguinity (0.5 pts, PMID: 32994280), confirmed in trans with a pathogenic variant in one patient (c.734dup p.(Ser246Ter), 1.0 pt, PMID: 28403181), and in unconfirmed phase with a pathogenic variant in one patient (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 3299428). In two other patients, it was reported in unconfirmed phase with a variant classified as likely pathogenic by the VCEP (c.1319G>A p.(Arg440Gln), 0.25 pts, PMID: 33250842; c.2306G>C p.(Arg769Pro), 0.25 pts, PMID: 25987458) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness and reduced (<50%) or absent expression of calpain-3 protein in skeletal muscle, though the exact level was not specified (PMID: 22926650; PP4). This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting. The computational predictor REVEL gives a score of 0.872, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function. In addition, another missense variant at the same codon, c.1343G>A (p.Arg448His), has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy 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_Strong, PP4, PM2_Supporting, PP3, PM5.

Met criteria codes

PM5	✔	Another missense variant at the same codon, c.1343G>A (p.Arg448His), has been classified as Pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). c.1343G>A (p.Arg448His) is provisionally pathogenic without use of PM5 SpliceAI <0.5, no splice effect The Revel score for curated variant is >0.7 Not located near an exon-intron boundary.
PP3	✔	The computational predictor REVEL gives a score of 0.872, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function.
PP4	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness and reduced (<50%) or absent expression of calpain-3 protein in skeletal muscle, though the exact level was not specified (PMID: 22926650; PP4).
PM3_Strong	✔	This variant has been identified in at least six unrelated individuals with features consistent with LGMD (PMID: 25987458, 29797799, 22926650, 33250842, 32994280, 28403181), including in a homozygous state in one patient without reported consanguinity (0.5 pts, PMID: 32994280), confirmed in trans with a pathogenic variant in one patient (c.734dup p.(Ser246Ter), 1.0 pt, PMID: 28403181), and in unconfirmed phase with a pathogenic variant in one patient (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 3299428). In two other patients, it was reported in unconfirmed phase with a variant classified as likely pathogenic by the VCEP (c.1319G>A p.(Arg440Gln), 0.25 pts, PMID: 33250842; c.2306G>C p.(Arg769Pro), 0.25 pts, PMID: 25987458) (PM3_Strong). co-occurrence predictions for variants in unconfirmed phase c.2120A>G (p.Asp707Gly): predicted on different haplotype in gnomAD v2 c.1319G>A (p.Arg440Gln): predicted on different haplotype in gnomAD v2 c.2306G>C p.(Arg769Pro): no prediction unscored cases: unknown phase with c.2243G>A (p.Arg748Gln) (not in VCI, Pathogenic in ClinVar) currently insufficient evidence to upgrade to PM3_Very Strong

PM2_Supporting	✔	This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting.

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.