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Variant: NM_000070.3(CAPN3):c.1319G>A (p.Arg440Gln)

Version: 1.0

CA347525

217147 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 45a4fbf0-c8c0-4fe6-a6d3-e42c01718458
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3:c.1319G>A
NM_000070.3(CAPN3):c.1319G>A (p.Arg440Gln)
NC_000015.10:g.42399617G>A
CM000677.2:g.42399617G>A
NC_000015.9:g.42691815G>A
CM000677.1:g.42691815G>A
NC_000015.8:g.40479107G>A
NG_008660.1:g.56515G>A
ENST00000349748.8:c.1175G>A
ENST00000357568.8:c.1319G>A
ENST00000397163.8:c.1319G>A
ENST00000466369.5:n.1828G>A
ENST00000483208.5:n.1550G>A
ENST00000495723.1:n.1550G>A
ENST00000549793.5:n.1550G>A
ENST00000638141.2:n.1190G>A
ENST00000673658.1:n.303G>A
ENST00000673705.1:c.274G>A
ENST00000318023.11:c.1175G>A
ENST00000349748.7:c.1175G>A
ENST00000357568.7:c.1319G>A
ENST00000397163.7:c.1319G>A
NM_000070.2:c.1319G>A
NM_024344.1:c.1319G>A
NM_173087.1:c.1175G>A
NM_024344.2:c.1319G>A
NM_173087.2:c.1175G>A

Likely Pathogenic

Met criteria codes 3

PP4_Strong PM3_Strong PP3

Not Met criteria codes 1

PM2

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 1.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.1319G>A variant in CAPN3 is a missense variant predicted to cause the substitution of arginine by glutamine at amino acid 440 (p.Arg440Gln). This variant has been detected in at least 12 individuals with a clinical diagnosis or suspicion of limb girdle muscular dystrophy (PMID: 20694146, 18055493, 17994539, 18334579, 18854869, 15689361, 19048948, 21984748; Washington University internal clinic data communication), including confirmed in trans with a pathogenic variant (c.550del, 1.0 pt, PMID: 17994539), and in unknown phase with a likely pathogenic or pathogenic variant in three cases (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, PMID: 21984748; c.633G>C p.(Lys211Asn), 0.5 pts, PMID: 18334579, 20694146, 18055493) (PM3_Strong). At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed absent calpain-3 protein expression, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 18055493, 20694146, 18854869, 19048948). The filtering allele frequency of the variant is 0.0004336 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 7/30318), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). The computational predictor REVEL gives a score of 0.79, which is above the 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 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 1.0.0; 01/09/2025): PM3_Strong, PP4_Strong, PP3.

Met criteria codes

PP4_Strong	✔	At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed absent calpain-3 protein expression, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 18055493, 20694146, 18854869, 19048948).
PM3_Strong	✔	This variant has been detected in at least 12 individuals with a diagnosis or clinical suspicion of limb girdle muscular dystrophy (PMID: 20694146, 18055493, 17994539, 18334579, 18854869, 15689361, 19048948, 21984748; Washington University internal data), including confirmed in trans with a pathogenic variant (c.550del, 1.0 pt, PMID: 17994539), and in unknown phase with a likely pathogenic or pathogenic variant in three cases (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, PMID: 21984748; c.633G>C p.(Lys211Asn), 0.5 pts, PMID: 18334579, 20694146, 18055493) (PM3_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.79, which is above the VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3).

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variant is 0.0004336 for South Asian exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 7/30318), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000070.3(CAPN3):c.1319G>A (p.Ar...	Likely Pathogenic	Autosomal Recessive Limb-Girdle Muscular Dystrophy	2025-01-09	1.0	ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CAPN3 Version 1.0.0	CAPN3

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