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Variant: NM_000070.3(CAPN3):c.1469G>A (p.Arg490Gln)

Version: 1.0

CA341479

17622 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d235fd78-cdd6-4aed-9d55-bc0a90ba72ce
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3(CAPN3):c.1469G>A (p.Arg490Gln)
NM_000070.3:c.1469G>A
NC_000015.10:g.42401755G>A
CM000677.2:g.42401755G>A
NC_000015.9:g.42693953G>A
CM000677.1:g.42693953G>A
NC_000015.8:g.40481245G>A
NG_008660.1:g.58653G>A
ENST00000349748.8:c.1325G>A
ENST00000357568.8:c.1469G>A
ENST00000397163.8:c.1469G>A
ENST00000466369.5:n.1978G>A
ENST00000483208.5:n.1700G>A
ENST00000495723.1:n.1700G>A
ENST00000549793.5:n.1700G>A
ENST00000638141.2:n.1340G>A
ENST00000673705.1:c.309+2103G>A
ENST00000318023.11:c.1325G>A
ENST00000349748.7:c.1325G>A
ENST00000357568.7:c.1469G>A
ENST00000397163.7:c.1469G>A
NM_000070.2:c.1469G>A
NM_024344.1:c.1469G>A
NM_173087.1:c.1325G>A
NM_024344.2:c.1469G>A
NM_173087.2:c.1325G>A

Pathogenic

Met criteria codes 4

PM5 PM3_Very Strong PP3 PP4

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.1469G>A variant in CAPN3 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 490 (p.Arg440Gln). This variant has been detected in at least 16 individuals with limb girdle muscular dystrophy (PMID: 26404900, 18055493, 10330340, 22378277, 22443334, 18854869), including in a homozygous state in at least four cases (1.0 pt; PMID: 18055493, 10330340, 22443334) and confirmed in trans with a pathogenic variant in three cases (c.550del p.(Thr184ArgfsTer36), 3.0 pts, PMID: 26404900, 18854869, 22378277) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4). The highest population minor allele frequency of this variant is 0.0001846 (3/16248 exome alleles) in the African/African American population in gnomAD v2.1.1, which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). The computational predictor REVEL gives a score of 0.94, which is above the VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3). Another missense variant at the same codon, c.1468C>T p.(Arg490Trp), 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 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_Very Strong, PP4, PP3, PM5.

Met criteria codes

PM5	✔	Another missense variant at the same codon, c.1468C>T p.(Arg490Trp), has been classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5).
PM3_Very Strong	✔	This variant has been detected in at least 16 individuals with limb girdle muscular dystrophy (PMID: 26404900, 18055493, 10330340, 22378277, 22443334, 18854869), including in a homozygous state in at least four cases (1.0 pt; PMID: 18055493, 10330340, 22443334) and confirmed in trans with a pathogenic variant in three cases (c.550del p.(Thr184ArgfsTer36), 3.0 pts, PMID: 26404900, 18854869, 22378277) (PM3_Very Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.94, which is above the VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3).
PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4).

Not Met criteria codes

PM2	✖	The highest population minor allele frequency of this variant is 0.0001846 (3/16248 exome alleles) in the African/African American population in gnomAD v2.1.1, which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

Showing 1 to 1 of 1 rows

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