Variant: NM_000070.3(CAPN3):c.1468C>T (p.Arg490Trp)

Version: 1.0

CA233621

166790 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: f5c5423d-bf69-46d6-b064-d43133637e25
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HGVS expressions

NM_000070.3:c.1468C>T
NM_000070.3(CAPN3):c.1468C>T (p.Arg490Trp)
NC_000015.10:g.42401754C>T
CM000677.2:g.42401754C>T
NC_000015.9:g.42693952C>T
CM000677.1:g.42693952C>T
NC_000015.8:g.40481244C>T
NG_008660.1:g.58652C>T
ENST00000349748.8:c.1324C>T
ENST00000357568.8:c.1468C>T
ENST00000397163.8:c.1468C>T
ENST00000466369.5:n.1977C>T
ENST00000483208.5:n.1699C>T
ENST00000495723.1:n.1699C>T
ENST00000549793.5:n.1699C>T
ENST00000638141.2:n.1339C>T
ENST00000673705.1:c.309+2102C>T
ENST00000318023.11:c.1324C>T
ENST00000349748.7:c.1324C>T
ENST00000357568.7:c.1468C>T
ENST00000397163.7:c.1468C>T
NM_000070.2:c.1468C>T
NM_024344.1:c.1468C>T
NM_173087.1:c.1324C>T
NM_024344.2:c.1468C>T
NM_173087.2:c.1324C>T

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP3 | PP4_Moderate

Not Met criteria codes 2

PS3 | PM2

Evidence Links 2

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.1468C>T variant in CAPN3 is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 490 (p.Arg490Trp). This variant has been detected in at least 18 individuals with limb girdle muscular dystrophy (PMID: 18055493, 10330340, 25214167, 25135358, 26632398, 12461690, 17994539), including in a homozygous state in at least two cases (1.0 pt; PMID: 18055493), confirmed in trans with a pathogenic variant in one case (c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 17994539), and in unknown phase with a pathogenic variant in four cases c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 25135358; c.2279dup p.(Asn760LysfsTer5), 0.5 pts, PMID: 18055493; c.2242C>T p.(Arg748Ter), 0.5 pts, PMID: 25214167) (PM3_Very Strong). At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PP4_Moderate; PMID: 17994539). The highest population minor allele frequency of this variant is 0.0004598 (4/8700 genome 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 0.84, 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 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_Moderate, PP3.

Met criteria codes

PM3_Very Strong	✔	This variant has been detected in at least 18 individuals with limb girdle muscular dystrophy (PMID: 18055493, 10330340, 25214167, 25135358, 26632398, 12461690, 17994539), including in a homozygous state in at least two cases (1.0 pt; PMID: 18055493), confirmed in trans with a pathogenic variant in one case (c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 17994539), and in unknown phase with a pathogenic variant in four cases c.550del p.(Thr184ArgfsTer36), 1.0 pt, PMID: 25135358; c.2279dup p.(Asn760LysfsTer5), 0.5 pts, PMID: 18055493; c.2242C>T p.(Arg748Ter), 0.5 pts, PMID: 25214167) (PM3_Very Strong). Note: c.1468C>T p.(Arg490Trp) and c.2242C>T p.(Arg748Ter) predicted to be on different haplotypes by gnomAD. Different cases scored to get both variants to P.
PP3	✔	The computational predictor REVEL gives a score of 0.84, which is above the VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3).
PP4_Moderate	✔	At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy and displayed reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PP4_Moderate; PMID: 17994539).

Not Met criteria codes

PS3	✖	Functional assays have suggested this variant reduces calpain-3 autocatalytic activity (PMID: 14578192, 9642272), but the LGMD VCEP has determined that this type of assay has not yet been sufficiently validated. Functional assay demonstrating that variants cause changes in autolytic activity and/or connectin/titin binding activity. When transfected into COS7 cells along with wildtype human protein, the R490W variant reduced the autolytic activity by lowering the Ca2+ sensitivity. Not scoreable under PS3 using current specifications. PubMed:9642272

Show that the variant impairs the autocatalytic activity of the protein, slowing protein degradation as compared to controls. Not scorable under PS3 using current specifications. PubMed:14578192

PM2	✖	The highest population minor allele frequency of this variant is 0.0004598 (4/8700 genome 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

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