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.2242C>T (p.Arg748Ter)

Version: 1.0

CA7511779

283259 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d6fb54e2-b3a3-46d1-bf4d-0bf57f2e3a7d
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3:c.2242C>T
NM_000070.3(CAPN3):c.2242C>T (p.Arg748Ter)
NC_000015.10:g.42410645C>T
CM000677.2:g.42410645C>T
NC_000015.9:g.42702843C>T
CM000677.1:g.42702843C>T
NC_000015.8:g.40490135C>T
NG_008660.1:g.67543C>T
ENST00000337571.9:c.247C>T
ENST00000349748.8:c.1966C>T
ENST00000357568.8:c.2224C>T
ENST00000397163.8:c.2242C>T
ENST00000397204.9:c.247C>T
ENST00000466222.7:n.598C>T
ENST00000466369.5:n.2733C>T
ENST00000495723.1:n.3113C>T
ENST00000549793.5:n.2455C>T
ENST00000562199.2:c.246C>T
ENST00000567817.6:c.31C>T
ENST00000568153.2:c.108C>T
ENST00000569136.6:c.247C>T
ENST00000638141.2:n.1981C>T
ENST00000673646.1:c.806C>T
ENST00000673684.1:n.224C>T
ENST00000673687.1:n.842C>T
ENST00000673692.1:c.247C>T
ENST00000673705.1:c.568C>T
ENST00000673743.1:c.145C>T
ENST00000673750.1:c.247C>T
ENST00000673771.1:c.247C>T
ENST00000673774.1:n.1375C>T
ENST00000673839.1:c.247C>T
ENST00000673851.1:c.247C>T
ENST00000673854.1:n.5664C>T
ENST00000673886.1:c.247C>T
ENST00000673890.1:c.247C>T
ENST00000673928.1:c.247C>T

ENST00000673936.1:c.247C>T
ENST00000673939.1:c.247C>T
ENST00000673950.1:n.516C>T
ENST00000673978.1:c.385C>T
ENST00000673987.1:c.247C>T
ENST00000674011.1:c.247C>T
ENST00000674018.1:c.247C>T
ENST00000674027.1:n.393C>T
ENST00000674041.1:c.247C>T
ENST00000674052.1:c.466C>T
ENST00000674093.1:c.247C>T
ENST00000674119.1:c.247C>T
ENST00000674135.1:c.424C>T
ENST00000674139.1:c.247C>T
ENST00000674146.1:c.247C>T
ENST00000674149.1:c.247C>T
ENST00000318023.11:c.2098C>T
ENST00000337571.8:c.247C>T
ENST00000349748.7:c.1966C>T
ENST00000356316.7:c.247C>T
ENST00000357568.7:c.2224C>T
ENST00000397163.7:c.2242C>T
ENST00000397200.8:c.706C>T
ENST00000397204.8:c.247C>T
ENST00000466222.6:n.1165C>T
ENST00000561817.5:c.247C>T
ENST00000562199.1:n.246C>T
ENST00000564503.5:c.285C>T
ENST00000565274.5:c.420C>T
ENST00000565559.5:c.424C>T
ENST00000567817.5:c.58C>T
ENST00000569136.5:c.247C>T
ENST00000569827.5:c.574C>T
NM_000070.2:c.2242C>T
NM_024344.1:c.2224C>T
NM_173087.1:c.1966C>T
NM_173088.1:c.706C>T
NM_173089.1:c.247C>T
NM_173090.1:c.247C>T
NM_024344.2:c.2224C>T
NM_173087.2:c.1966C>T
NM_173088.2:c.706C>T
NM_173089.2:c.247C>T
NM_173090.2:c.247C>T

Pathogenic

Met criteria codes 3

PVS1 PP4_Moderate PM3

Not Met criteria codes 1

PM2

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Evidence Links 0

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.2242C>T p.(Arg748Ter) variant in CAPN3, which is also known as p.(Arg748del), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 21/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism. mRNA analysis demonstrated reduced expression of the transcript containing the variant, consistent with nonsense mediated decay (PMID: 17157502) (PVS1). This variant has been detected in at least six individuals reported to have autosomal recessive LGMD (PMID: 25214167, 12461690, 16971480, 17157502, 18055493; Washington University internal clinic data communication). In at least one case, the variant was identified in unknown phase with a pathogenic variant (c.1468C>T p.(Arg490Trp), 0.5 pts, PMID: 16971480), and in at least two cases, the variant was identified in trans with a second CAPN3 variant not yet curated by the VCEP and considered VUS (0.5 pts, PMID: 12461690, 17157502) (PM3). 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: 16971480). The filtering allele frequency of the variant is 0.000114 for European (non-Finnish) genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 3/68008), which is more than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). 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): PVS1, PM3, PP4_Moderate.

Met criteria codes

PVS1	✔	The NM_000070.3: c.2242C>T p.(Arg748Ter) variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 21/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. mRNA analysis demonstrated reduced expression of the transcript containing the variant, consistent with nonsense mediated decay (PMID: 17157502) (PVS1).
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: 16971480).
PM3	✔	This variant has been detected in at least six individuals reported to have autosomal recessive LGMD (PMID: 25214167, 12461690, 16971480, 17157502, 18055493; Washington University internal data). In at least one case, the variant was identified in unknown phase with a pathogenic variant (c.1468C>T p.(Arg490Trp), 0.5 pts, PMID: 16971480), and in at least two cases, the variant was identified in trans with a second CAPN3 variant not yet curated by the VCEP and considered VUS (0.5 pts, PMID: 12461690, 17157502; Washington University internal data) (PM3). 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.

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variant is 0.000114 for European (non-Finnish) genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 3/68008), which is more than the LGMD VCEP threshold (<0.0001) for

PM2_Supporting (criterion not met).

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.