

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

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HGVS expressions

NM_000070.3(CAPN3):c.2242C>T (p.Arg748Ter)

NM_000070.3:c.2242C>T

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

PP4_Moderate PVS1 PM3

Not Met criteria codes 1

PM2

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

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

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).
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).
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
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PM2_Supporting (criterion not met).

Curation History



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