

Variant: *NM_000070.3(CAPN3):c.328C>T (p.Arg110Ter)*

Version: 1.0

CA341471 [↗](#)

17615 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))

Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 042a61fa-0733-4208-9bcf-82ea00d74c79

Approved on: 2025/1/7

Published on: 2025/1/7

HGVS expressions

NM_000070.3:c.328C>T

NM_000070.3(CAPN3):c.328C>T (p.Arg110Ter)

NC_000015.10:g.42384501C>T

CM000677.2:g.42384501C>T

NC_000015.9:g.42676699C>T

CM000677.1:g.42676699C>T

NC_000015.8:g.40463991C>T

NG_008660.1:g.41399C>T

ENST00000349748.8:c.328C>T

ENST00000357568.8:c.328C>T

ENST00000397163.8:c.328C>T

ENST00000466369.5:n.559C>T

ENST00000483208.5:n.559C>T

ENST00000495723.1:n.559C>T

ENST00000549793.5:n.559C>T

ENST00000638141.2:n.343C>T

ENST00000673705.1:c.19C>T

ENST00000318023.11:c.328C>T

ENST00000349748.7:c.328C>T

ENST00000357568.7:c.328C>T

ENST00000397163.7:c.328C>T

NM_000070.2:c.328C>T

NM_024344.1:c.328C>T

NM_173087.1:c.328C>T

NM_024344.2:c.328C>T

NM_173087.2:c.328C>T

Pathogenic

Met criteria codes 4

PP4_Moderate

PVS1

PP1

PM2_Supporting

Not Met criteria codes 22

BA1

BS2

BS1

BS4

BS3

BP5

BP7

BP4

BP3

BP1

BP2

PS1

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

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.328C>T p.(Arg110Ter) variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 2/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in trans with a second CAPN3 variant in at least three unrelated individuals with LGMD (PMID: 26677118, 18854869). At least one patient with this variant displayed progressive limb girdle muscle weakness and reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PP4_Moderate; PMID: 18854869). The variant has also been reported to co-segregate with the disease in one affected family member (PP1; PMID: 26677118). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008793 (1/113722 exome alleles) in the European (non-Finnish) population, which is less than the VCEP threshold (≤ 0.0001) (PM2_Supporting). 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; 01/07/2025): PVS1, PP4_Moderate, PP1, PM2_Supporting.

Met criteria codes

PP4_Moderate			At least one patient with this variant displayed progressive limb girdle muscle weakness and reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PP4_Moderate; PMID: 18854869).
PVS1			The c.328C>T p.(Arg110Ter) variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 2/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP1			The variant has been reported to c-segregate with the disease in one affected family member (PP1; PMID: 26677118).
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.000008793 (1/113722 exome alleles) in the European (non-Finnish) population, which is less than the ClinGen LGMD threshold (≤ 0.0001) (PM2_Supporting).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

