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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

PVS1 PP4_Moderate PM2_Supporting PP1

Not Met criteria codes 22

BS2 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7 PM1

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*

PM3 PM5 BA1 PM4 PM6
PS1 PS2 PS3 PS4 PP2 PP3

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence Links 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

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).
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).
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).
PP1	✔	The variant has been reported to c-segregate with the disease in one affected family member (PP1; PMID: 26677118).

Not Met criteria codes

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
BP4	ℹ	✖	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	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✖	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
PS1	ℹ	✖	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

Curation History

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