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Variant: NM_000070.3(CAPN3):c.145C>T (p.Arg49Cys)

Version: 1.0

CA346852

193037 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 02c8c70e-5a36-40bb-b81e-534e414b6839
Approved on: 2026/4/29
Published on: 2026/5/7

HGVS expressions

NM_000070.3:c.145C>T
NM_000070.3(CAPN3):c.145C>T (p.Arg49Cys)
NC_000015.10:g.42359950C>T
CM000677.2:g.42359950C>T
NC_000015.9:g.42652148C>T
CM000677.1:g.42652148C>T
NC_000015.8:g.40439440C>T
NG_008660.1:g.16848C>T
ENST00000349748.8:c.145C>T
ENST00000357568.8:c.145C>T
ENST00000397163.8:c.145C>T
ENST00000466369.5:n.540+5497C>T
ENST00000483208.5:n.540+5497C>T
ENST00000495723.1:n.540+5497C>T
ENST00000549793.5:n.540+5497C>T
ENST00000318023.11:c.145C>T
ENST00000349748.7:c.145C>T
ENST00000357568.7:c.145C>T
ENST00000397163.7:c.145C>T
NM_000070.2:c.145C>T
NM_024344.1:c.145C>T
NM_173087.1:c.145C>T
NM_024344.2:c.145C>T
NM_173087.2:c.145C>T

Pathogenic

Met criteria codes 4

PP3 PM5 PP4_Strong PM3_Strong

Not Met criteria codes 1

PM2

Evidence Links 0

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 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.145C>T variant in CAPN3 is a missense variant predicted to cause the substitution of arginine by cysteine at amino acid position 49, p.(Arg49Cys). This variant has been detected in at least six unrelated individuals with limb girdle muscular dystrophy (PMID: 35198268, 19285864, 19556129, 28403181, 31862442), including in a homozygous state in one individual with known consanguinity (PMID: 19285864, 0.25 pts), confirmed in trans with a pathogenic variant (c.2120A>G p.(Asp707Gly), 1.0 pt, PMID: 28403181), and in unknown phase with a second pathogenic variant in two individuals (c.2242C>T p.(Arg748Ter), 0.5 pt, PMID: 35198268; c.1468C>T p.(Arg490Trp), 0.5 pt, PMID: 19556129) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 35198268, 19556129). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0001005 (4/91080 South Asian alleles), which is greater than the VCEP threshold of 0.0001 (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.734, which is above the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). In addition, another missense variant at the same codon, c.146G>A p.(Arg49His), has been classified as pathogenic by the ClinGen LGMD VCEP (PM5). 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 2.0.0; 04/29/2026): PM3_Strong, PP4_Strong, PM5, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.734, which is above the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). No predicted impact on Splicing
PM5	✔	Another missense variant at the same codon, c.146G>A p.(Arg49His), has been classified as pathogenic by the ClinGen LGMD VCEP (PM5). both variants have REVEL scores above PP3 threshold neither is predicted to affect splicing The NM_000070.3: c.146G>A variant in CAPN3 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 49 (p.Arg49His). This variant has been detected in at least six unrelated individuals with limb girdle muscular dystrophy (PMID: 16650086, 17318636, 25135358; ClinVar SCV003459936.1 internal data communication, ClinVar SCV001164521.1 internal data communication), including in a homozygous state in one individual (ClinVar SCV001164521.1 internal data communication, 0.5 pts), confirmed in trans with a pathogenic variant (c.967G>T p.(Glu323Ter), 1.0 pt, PMID: 17318636), and confirmed in trans with two variants not yet curated by the VCEP and considered VUS (0.5 pts) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 16650086). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.84, which exceeds 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_Strong, PP4_Strong, PM2_Supporting, PP3.
PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 35198268, 19556129).
PM3_Strong	✔	This variant has been detected in at least six unrelated individuals with limb girdle muscular dystrophy (PMID: 35198268, 19285864, 19556129, 28403181, 31862442), including in a homozygous state in one individual with known consanguinity (PMID: 19285864, 0.25 pts), confirmed in trans with a pathogenic variant (c.2120A>G p.

(Asp707Gly), 1.0 pt, PMID: 28403181), and in unknown phase with a second pathogenic variant in two individuals (c.2242C>T p.(Arg748Ter), 0.5 pt, PMID: 35198268; c.1468C>T p.(Arg490Trp), 0.5 pt, PMID: 19556129) (PM3_Strong). predicted on different haplotypes with c.1468C>T p.(Arg490Trp) and c.2242C>T p.(Arg748Ter)

Not Met criteria codes

PM2	✖	The upper bound of the 95% confidence interval of the Grpmax variant allele frequency in gnomAD v4.1.1 is 0.0001005 (4/91080 South Asian alleles), which is greater than the VCEP threshold of 0.0001 (PM2_Supporting not met). Criterion met with European (non-Finnish) and East Asian data but not with South Asian data but code not needed for P classification.

Curation History

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