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Variant: NM_000070.3(CAPN3):c.2182C>T (p.Gln728Ter)

Version: 1.0

CA392001751

871348 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 164de678-9f75-417e-bd16-d1d916c5c1c8
Approved on: 2026/2/10
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HGVS expressions

NM_000070.3:c.2182C>T
NM_000070.3(CAPN3):c.2182C>T (p.Gln728Ter)
NC_000015.10:g.42410494C>T
CM000677.2:g.42410494C>T
NC_000015.9:g.42702692C>T
CM000677.1:g.42702692C>T
NC_000015.8:g.40489984C>T
NG_008660.1:g.67392C>T
ENST00000337571.9:c.187C>T
ENST00000349748.8:c.1906C>T
ENST00000357568.8:c.2164C>T
ENST00000397163.8:c.2182C>T
ENST00000397204.9:c.187C>T
ENST00000466222.7:n.447C>T
ENST00000466369.5:n.2673C>T
ENST00000495723.1:n.3053C>T
ENST00000549793.5:n.2395C>T
ENST00000562199.2:c.186C>T
ENST00000568153.2:c.48C>T
ENST00000569136.6:c.187C>T
ENST00000638141.2:n.1921C>T
ENST00000673646.1:c.746C>T
ENST00000673684.1:n.164C>T
ENST00000673687.1:n.691C>T
ENST00000673692.1:c.187C>T
ENST00000673705.1:c.511-94C>T
ENST00000673743.1:c.85C>T
ENST00000673750.1:c.187C>T
ENST00000673771.1:c.187C>T
ENST00000673774.1:n.1315C>T
ENST00000673839.1:c.187C>T
ENST00000673851.1:c.187C>T
ENST00000673854.1:n.5604C>T
ENST00000673886.1:c.187C>T
ENST00000673890.1:c.187C>T
ENST00000673893.1:c.385C>T
ENST00000673928.1:c.187C>T

ENST00000673936.1:c.187C>T
ENST00000673939.1:c.187C>T
ENST00000673950.1:n.456C>T
ENST00000673978.1:c.325C>T
ENST00000673987.1:c.187C>T
ENST00000674011.1:c.187C>T
ENST00000674018.1:c.187C>T
ENST00000674027.1:n.242C>T
ENST00000674041.1:c.187C>T
ENST00000674052.1:c.406C>T
ENST00000674093.1:c.187C>T
ENST00000674119.1:c.187C>T
ENST00000674135.1:c.364C>T
ENST00000674139.1:c.187C>T
ENST00000674146.1:c.187C>T
ENST00000674149.1:c.187C>T
ENST00000318023.11:c.2038C>T
ENST00000337571.8:c.187C>T
ENST00000349748.7:c.1906C>T
ENST00000356316.7:c.187C>T
ENST00000357568.7:c.2164C>T
ENST00000397163.7:c.2182C>T
ENST00000397200.8:c.646C>T
ENST00000397204.8:c.187C>T
ENST00000466222.6:n.1105C>T
ENST00000561817.5:c.187C>T
ENST00000562199.1:n.186C>T
ENST00000564503.5:c.279C>T
ENST00000565274.5:c.414C>T
ENST00000565559.5:c.364C>T
ENST00000569136.5:c.187C>T
ENST00000569827.5:c.514C>T
NM_000070.2:c.2182C>T
NM_024344.1:c.2164C>T
NM_173087.1:c.1906C>T
NM_173088.1:c.646C>T
NM_173089.1:c.187C>T
NM_173090.1:c.187C>T
NM_024344.2:c.2164C>T
NM_173087.2:c.1906C>T
NM_173088.2:c.646C>T
NM_173089.2:c.187C>T
NM_173090.2:c.187C>T

Pathogenic

Met criteria codes 5

PM2_Supporting PP1 PP4 PVS1 PM3_Supporting

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.2182C>T p.(Gln728Ter) variant in CAPN3 is a nonsense variant expected to cause a premature stop codon in biologically relevant exon 20/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism. However, this variant affects the last amino acid of the exon and is also predicted to affect splicing, including loss of the canonical donor site (SpliceAI delta score 0.82, alt score 0.06) and strengthening of an alternative donor site 4 nucleotides into exon 24 (SpliceAI delta score 0.96, alt score 0.97). Use of the alternative donor would also be expected to result in a frameshift and nonsense mediated decay (PVS1). This variant has been identified in at least three unrelated individuals with clinical features consistent with limb-girdle muscular dystrophy (PMID: 30919934, 17562833), including in a homozygous state with known consanguinity (0.25 pts, PMID: 30919934, 17562833) and in unconfirmed phase with a variant independently classified as likely pathogenic (c.1466G>A (p.Arg489Gln), 0.25 pts, PMID: 30919934) (PM3_Supporting). At least one individual with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 30919934; PP4). This variant has also been reported to co-segregate with the autosomal recessive LGMD phenotype in one affected family member (PMID: 17562833, 30919934; PP1). The highest population allele frequency of this variant is 0.000013354 in the African/African-American population of gnomAD v4.1.0 (1/74884 chromosomes), which is less than the ClinGen LGMD 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 criteria applied, as specified by the LGMD VCEP (specifications version 2.0.0; 02/10/2026): PVS1, PM3_Supporting, PP4, PP1, PM2_Supporting.

Met criteria codes

PM2_Supporting ✔	The highest population allele frequency of this variant is 0.000013354 in the African/African-American population of gnomAD v4.1.0 (1/74884 chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).
PP1 ✔	This variant has also been reported to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 17562833, 30919934); PP1).
PP4 ✔	At least one individual with this variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 30919934; PP4).
PVS1 ✔	The NM_000070.3: c.2182C>T p.(Gln728Ter) variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 20/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism. However, this variant affects the last amino acid of the exon and is also predicted to affect splicing, including loss of the canonical donor site (SpliceAI delta score 0.82, alt score 0.06) and strengthening of an alternative donor site 4 nucleotides into exon 24 (SpliceAI delta score 0.96, alt score 0.97). Use of the alternative donor would also be expected to result in a frameshift and nonsense mediated decay (PVS1). GENEie: 75% probability splice altering NIF impact U5 -81% U1 -46% U6 0% use of the cryptic donor at -4 is found in 52 samples in SpliceVault.
PM3_Supporting ✔	This variant has been identified in at least three unrelated individuals with clinical features consistent with limb-girdle muscular dystrophy (PMID: 30919934, 17562833), including in a homozygous state with known consanguinity (0.25 pts, PMID: 30919934, 17562833) and in unconfirmed phase with a variant independently classified as likely

pathogenic (c.1466G>A (p.Arg489Gln), 0.25 pts, PMID: 30919934). c.2182C>T (p.Gln728Ter) not found in gnomAD v2 and so co-occurrence cannot be checked. c.1466G>A (p.Arg489Gln) can be classified as LP without counting data from the case where it co-occurs with c.2182C>T (p.Gln728Ter)

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000070.3(CAPN3):c.2182C>T (p.Gl...	Pathogenic	Autosomal Recessive Limb-Girdle Muscular Dystrophy	2026-02-17	1.0	ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CAPN3 Version 2.0.0	CAPN3

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