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Variant: NM_000070.3(CAPN3):c.1855C>T (p.Gln619Ter)

Version: 1.0

CA392000775

595306 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: bda99519-5ab7-4bac-a96b-9a3ded3b8556
Approved on: 2025/10/28
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HGVS expressions

NM_000070.3(CAPN3):c.1855C>T (p.Gln619Ter)
NM_000070.3:c.1855C>T
NC_000015.10:g.42408265C>T
CM000677.2:g.42408265C>T
NC_000015.9:g.42700463C>T
CM000677.1:g.42700463C>T
NC_000015.8:g.40487755C>T
NG_008660.1:g.65163C>T
ENST00000337571.9:c.-81-1038C>T
ENST00000349748.8:c.1639-1038C>T
ENST00000357568.8:c.1837C>T
ENST00000397163.8:c.1855C>T
ENST00000397204.9:c.-81-1038C>T
ENST00000466369.5:n.2346C>T
ENST00000495723.1:n.2726C>T
ENST00000549793.5:n.2068C>T
ENST00000565173.2:n.229C>T
ENST00000569136.6:c.-141C>T
ENST00000638141.2:n.1654-1038C>T
ENST00000673646.1:c.419C>T
ENST00000673692.1:c.-3-1522C>T
ENST00000673705.1:c.310-1038C>T
ENST00000673743.1:c.-179+125C>T
ENST00000673750.1:c.-141C>T
ENST00000673771.1:c.-141C>T
ENST00000673839.1:c.-285C>T
ENST00000673851.1:c.-141C>T
ENST00000673854.1:n.4299C>T
ENST00000673886.1:c.-141C>T
ENST00000673890.1:c.-141C>T
ENST00000673928.1:c.-82+125C>T
ENST00000673936.1:c.-141C>T
ENST00000673939.1:c.-81-1038C>T
ENST00000673978.1:c.-307C>T
ENST00000673987.1:c.-141C>T
ENST00000674011.1:c.-141C>T
ENST00000674012.1:n.130C>T

ENST00000674018.1:c.-141C>T
ENST00000674041.1:c.-81-1038C>T
ENST00000674052.1:c.79C>T
ENST00000674064.1:n.234C>T
ENST00000674093.1:c.-81-1038C>T
ENST00000674119.1:c.-81-1038C>T
ENST00000674135.1:c.-77C>T
ENST00000674139.1:c.-141C>T
ENST00000674140.1:n.1006C>T
ENST00000674146.1:c.-141C>T
ENST00000674149.1:c.-141C>T
ENST00000318023.11:c.1711C>T
ENST00000337571.8:c.-81-1038C>T
ENST00000349748.7:c.1639-1038C>T
ENST00000356316.7:c.-90-1029C>T
ENST00000357568.7:c.1837C>T
ENST00000397163.7:c.1855C>T
ENST00000397200.8:c.319C>T
ENST00000397204.8:c.-81-1038C>T
ENST00000561817.5:c.-81-1038C>T
ENST00000565173.1:n.184C>T
ENST00000565274.5:c.67C>T
ENST00000565559.5:c.-77C>T
ENST00000567071.5:c.314C>T
ENST00000569136.5:c.-141C>T
ENST00000569827.5:c.247-1038C>T
NM_000070.2:c.1855C>T
NM_024344.1:c.1837C>T
NM_173087.1:c.1639-1038C>T
NM_173088.1:c.319C>T
NM_173089.1:c.-81-1038C>T
NM_173090.1:c.-81-1038C>T
NM_024344.2:c.1837C>T
NM_173087.2:c.1639-1038C>T
NM_173088.2:c.319C>T
NM_173089.2:c.-81-1038C>T
NM_173090.2:c.-81-1038C>T

Likely Pathogenic

Met criteria codes 4

PVS1_Strong PP4 PM3 PM2_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.1855C>T variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 16/24, p.(Gln619Ter), leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism. However, this variant may also disrupt splicing, with a SpliceAI score of 0.64 for donor loss and 0.58 for acceptor loss, suggesting that in-frame skipping of exon 16 may occur. (PVS1_Strong) This variant has been reported in at least 6 patients with features of LGMD (PMID: 25135358, 37974208, 32994280; ClinVar SCV001385372.6 internal data communication), including in a homozygous state in two unrelated individuals with a clinical diagnosis of LGMD and no reported familial consanguinity (0.5 pts x2, ClinVar SCV001385372.6 internal data communication) (PM3). At least one individual with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD (PMID: 37974208; PP4). This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting. In summary, this variant meets the criteria to be classified as Likely 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; 10/28/2025): PVS1_Strong, PM3, PP4, PM2_Supporting.

Met criteria codes

PVS1_Strong	✔	The NM_000070.3:c.1855C>T (p.Gln619Ter) variant in CAPN3 is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 16/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism. However, this variant may also disrupt splicing, with a SpliceAI score of 0.64 for donor loss and 0.58 for acceptor loss, suggesting the potential for in-frame skipping of exon 16. SpliceAI : Acceptor loss: 0.58 -54 bp 0.94 0.36 Donor loss: 0.64 59 bp 0.76 0.12 SpliceAI predicts splice disruption with an acceptor loss score of 0.58 and donor loss score of 0.64, suggesting altered splicing could occur, but some degree of retained normal splicing possible as well. GENEie predicts that any resultant exon skipping would be in-frame, which introduces the possibility of a partially functional protein product rather than complete loss-of-function. Because this raises the possibility of a functional rescue mechanism, the strength is downgraded from PVS1 to PVS1_Strong, but the most conservative weight would be PVS1_Moderate assuming 100% in-frame exon skipping. Discussed at the 10/28/2025 VCEP call: group was comfortable with applying at either Moderate or Strong, acknowledging that it is difficult to predict the degree of missplicing that may occur since this variant likely disrupts a splice enhancer, and SpliceAI probability scores have not been specifically evaluated in this context. However, the group was also confident that skipping of exon 16 would be deleterious and was wary of being overly conservative. For these reasons, PVS1_Strong was applied.
PP4	✔	At least one individual with this variant displayed progressive limb girdle muscle weakness or had a clinical suspicion of LGMD, PMID: 37974208. (Lin F, 2023)
PM3	✔	This variant has been reported in at least 6 patients with features of LGMD (PMID: 25135358, 37974208, 32994280; ClinVar SCV001385372.6 internal data communication), including in a homozygous state in two unrelated individuals with a clinical diagnosis of LGMD and no reported familial consanguinity (0.5 pts x2, ClinVar SCV001385372.6 internal data communication) (PM3). To get to pathogenic with PVS1_Strong, need 1.0 more PM3 pts c.245C>T (p.Pro82Leu), unknown phase: Pathogenic/Likely pathogenic in ClinVar, lots of lit c.77C>T (p.Pro26Leu), "compound heterozygous": VUS in ClinVar, at least one additional case c.2306G>C (p.Arg769Pro), unknown phase (this variant being curated to support curation): VUS/LP in ClinVar c.264T>G (p.Phe88Leu), unknown phase: P/LP/VUS in ClinVar, no citations Wait to decide whether to curate additional supporting variants until consensus on PVS1 strength.
PM2_Supporting	✔	This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting.

Curation History

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