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Variant: NM_000070.3(CAPN3):c.1981del (p.Gln660_Ile661insTer)

Version: 1.0

CA346859

194691 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9d7dffdf-e192-4264-8e82-93e8e48a47fb
Approved on: 2025/5/14
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HGVS expressions

NM_000070.3:c.1981delA
NM_000070.3(CAPN3):c.1981del (p.Gln660_Ile661insTer)
NM_000070.3:c.1981del
NC_000015.10:g.42409369del
CM000677.2:g.42409369del
NC_000015.9:g.42701567del
CM000677.1:g.42701567del
NC_000015.8:g.40488859del
NG_008660.1:g.66267del
ENST00000337571.9:c.-15del
ENST00000349748.8:c.1705del
ENST00000357568.8:c.1963del
ENST00000397163.8:c.1981del
ENST00000397204.9:c.-15del
ENST00000466222.7:n.246del
ENST00000466369.5:n.2472del
ENST00000495723.1:n.2852del
ENST00000549793.5:n.2194del
ENST00000569136.6:c.-15del
ENST00000638141.2:n.1720del
ENST00000673646.1:c.545del
ENST00000673687.1:n.58del
ENST00000673692.1:c.-3-418del
ENST00000673705.1:c.376del
ENST00000673743.1:c.-112del
ENST00000673750.1:c.-15del
ENST00000673771.1:c.-15del
ENST00000673774.1:n.276del
ENST00000673839.1:c.-159del
ENST00000673851.1:c.-15del
ENST00000673854.1:n.5403del
ENST00000673886.1:c.-15del
ENST00000673890.1:c.-15del
ENST00000673928.1:c.-15del
ENST00000673936.1:c.-15del

ENST00000673939.1:c.-15del
ENST00000673950.1:n.255del
ENST00000673978.1:c.124del
ENST00000673987.1:c.-15del
ENST00000674011.1:c.-15del
ENST00000674018.1:c.-15del
ENST00000674027.1:n.41del
ENST00000674041.1:c.-15del
ENST00000674052.1:c.205del
ENST00000674093.1:c.-15del
ENST00000674119.1:c.-15del
ENST00000674135.1:c.163del
ENST00000674139.1:c.-15del
ENST00000674146.1:c.-15del
ENST00000674149.1:c.-15del
ENST00000318023.11:c.1837del
ENST00000337571.8:c.-15del
ENST00000349748.7:c.1705del
ENST00000356316.7:c.-15del
ENST00000357568.7:c.1963del
ENST00000397163.7:c.1981del
ENST00000397200.8:c.445del
ENST00000397204.8:c.-15del
ENST00000466222.6:n.904del
ENST00000561817.5:c.-15del
ENST00000564503.5:c.78del
ENST00000565274.5:c.193del
ENST00000565559.5:c.163del
ENST00000567071.5:c.461del
ENST00000569136.5:c.-15del
ENST00000569827.5:c.313del
NM_000070.2:c.1981del
NM_024344.1:c.1963del
NM_173087.1:c.1705del
NM_173088.1:c.445del
NM_173089.1:c.-15del
NM_173090.1:c.-15del
NM_024344.2:c.1963del
NM_173087.2:c.1705del
NM_173088.2:c.445del
NM_173089.2:c.-15del
NM_173090.2:c.-15del

Pathogenic

Met criteria codes 5

PP4 PP1_Strong PM3_Strong PM2_Supporting PVS1

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 1.0.0*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.1981del p.(Ile661Ter) variant in CAPN3, which is also known as p.(Gln660_Ile661insTer), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 17/24, 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 at least 11 patients with features consistent with LGMD (PMID: 30919934, 37526466, 19556129, 18337726, 18055493; LOVD CAPN3_000104), including confirmed in trans with a pathogenic variant in one individual (c.550del p.(Thr184Argfs36), 1.0 pt, PMID: 37526466), in unknown phase with a pathogenic variant in another individual (c.1838del p.(Lys613ArgfsTer49), 0.5 pts, PMID: 18055493), and in a homozygous state in an individual without reported familial consanguinity (0.5 pts, PMID: 18055493) (PM3_Strong). This variant has also been reported to co-segregate with autosomal recessive LGMD in four affected family members from two families (PMID: 30919934; PP1_Strong). In addition, at least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and severely reduced or absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 18337726, 19556129) (PP4, capped with PP1_Strong). The filtering allele frequency of this variant is 0.000061919 (the upper threshold of the 95% CI of 55/1111948 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold (≤0.0001), meeting this criterion (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; 05/14/2025): PVS1, PM3_Strong, PP1_Strong, PP4, PM2_Supporting.

Met criteria codes

PP4	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and severely reduced or absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 18337726, 19556129) (PP4, capped with PP1_Strong).
PP1_Strong	✔	This variant has been reported to co-segregate with autosomal recessive LGMD in four affected family members from two families (PMID: 30919934; PP1_Strong).
PM3_Strong	✔	The variant has been detected in at least 11 patients with features consistent with LGMD (PMID: 30919934, 37526466, 19556129, 18337726, 18055493; LOVD CAPN3_000104), including confirmed in trans with a pathogenic variant in one individual (c.550del p.(Thr184Argfs36), 1.0 pt, PMID: 37526466), in unknown phase with a pathogenic variant in another individual (c.1838del p.(Lys613ArgfsTer49), 0.5 pts, PMID: 18055493), and in a homozygous state in an individual without reported familial consanguinity (0.5 pts, PMID: 18055493) (PM3_Strong). c.1838del is absent from gnomAD v2 and so cannot check co-occurrence
PM2_Supporting	✔	The filtering allele frequency of this variant is 0.000061919 (the upper threshold of the 95% CI of 55/1111948 European (non-Finnish) exome chromosomes) in gnomAD v4.1.0, which is less than the ClinGen LGMD VCEP threshold for PM2_supporting (≤0.0001), meeting this criterion (PM2_Supporting).
PVS1	✔	The NM_000070.3: c.1981del p.(Ile661Ter) variant in CAPN3, which is also known as p.(Gln660_Ile661insTer), is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 17/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Curation History

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