Variant: NM_000070.3(CAPN3):c.550del (p.Thr184fs)

Version: 1.0

CA220352

17621 (ClinVar)

Gene: CAPN3
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 266d9a32-6af0-4d75-a5cd-deb6d7ab141e
Approved on: 2025-01-09
Published on: 2025-01-09

HGVS expressions

NM_000070.3:c.550delA
NM_000070.3:c.549delA
NM_000070.3:c.550del
NM_000070.3(CAPN3):c.550del (p.Thr184fs)
NC_000015.10:g.42387804del
CM000677.2:g.42387804del
NC_000015.9:g.42680002del
CM000677.1:g.42680002del
NC_000015.8:g.40467294del
NG_008660.1:g.44702del
ENST00000349748.8:c.550del
ENST00000357568.8:c.550del
ENST00000397163.8:c.550del
ENST00000466369.5:n.1059del
ENST00000483208.5:n.781del
ENST00000495723.1:n.781del
ENST00000549793.5:n.781del
ENST00000638141.2:n.565del
ENST00000673705.1:c.70+3252del
ENST00000318023.11:c.550del
ENST00000349748.7:c.550del
ENST00000357568.7:c.550del
ENST00000397163.7:c.550del
NM_000070.2:c.550del
NM_024344.1:c.550del
NM_173087.1:c.550del
NM_024344.2:c.550del
NM_173087.2:c.550del

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM3 PP1

Not Met criteria codes 1

PM2

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Evidence Links 0

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.550del p.(Thr184ArgfsTer36) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 5/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant is one of the most common disease-causing variants in CAPN3 reported in patients with Eastern European and Mediterranean ancestry (PMID: 25900067). It has been detected in at least 36 individuals with LGMD (PMID: 17236769, 17994539, 26404900, 30919934, 31788660, 17702496, 27142102). Of those individuals, at least 11 were compound heterozygous and 18 were homozygous (1.0 pt) (PM3). 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: 17236769). The variant has also been reported to segregate with LGMD in two affected family members from two families (PP1, capped with PP4_Strong; PMID: 30919934). The filtering allele frequency of the variant is 0.0005368 for European (non-Finnish) exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 48/113726), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). 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): PVS1, PM3, PP4_Strong, PP1.

Met criteria codes

PVS1	✔	The NM_000070.3: c.550delA p.(Thr184ArgfsTer36) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 5/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_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 DYSF (PP4_Strong; PMID: 17236769).
PM3	✔	This variant is one of the most common disease-causing variants in CAPN3 among Eastern European and Mediterranean populations (PMID: 25900067). It has been detected in at least 36 individuals with LGMD (PMID: 17236769, 17994539, 26404900, 30919934, 31788660, 17702496, 27142102). Of those individuals, at least 11 were compound heterozygous and 18 were homozygous (1.0 pt, PMID) (PM3).
PP1	✔	The variant has also been reported to segregate with LGMD in two affected family members from two families (PP1; PMID: 30919934). (capped with PP4_Strong)

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variant is 0.0005368 for European (non-Finnish) exome alleles in gnomAD v2.1.1 (the upper threshold of the 95% CI of 48/113726), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

Showing 1 to 1 of 1 rows