Variant: NM_000070.3(CAPN3):c.1187A>G (p.Glu396Gly)

Version: 1.0

CA7511268

497565 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5a841beb-d449-4064-89b8-0d234a741690
Approved on: 2025-04-22
Published on: 2025-05-16

HGVS expressions

NM_000070.3:c.1187A>G
NM_000070.3(CAPN3):c.1187A>G (p.Glu396Gly)
NC_000015.10:g.42396871A>G
CM000677.2:g.42396871A>G
NC_000015.9:g.42689069A>G
CM000677.1:g.42689069A>G
NC_000015.8:g.40476361A>G
NG_008660.1:g.53769A>G
ENST00000349748.8:c.1043A>G
ENST00000357568.8:c.1187A>G
ENST00000397163.8:c.1187A>G
ENST00000466369.5:n.1696A>G
ENST00000483208.5:n.1418A>G
ENST00000495723.1:n.1418A>G
ENST00000549793.5:n.1418A>G
ENST00000638141.2:n.1058A>G
ENST00000673658.1:n.171A>G
ENST00000673705.1:c.142A>G
ENST00000318023.11:c.1043A>G
ENST00000349748.7:c.1043A>G
ENST00000357568.7:c.1187A>G
ENST00000397163.7:c.1187A>G
NM_000070.2:c.1187A>G
NM_024344.1:c.1187A>G
NM_173087.1:c.1043A>G
NM_024344.2:c.1187A>G
NM_173087.2:c.1043A>G

Likely Pathogenic

Met criteria codes 4

PP4 PVS1_Strong PM3 PM2_Supporting

Not Met criteria codes 2

PP3 PM5

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP*

Evidence Links 0

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.1187A>G variant is CAPN3 is a missense variant predicted to cause substitution of glutamic acid by glycine at amino acid 396, p.(Glu396Gly). This variant affects the seventh nucleotide from the boundary of exon and intron 9 and has a SpliceAI score of 0.09 for gain of an alternative donor site in intron 9. Minigene assays have demonstrated a splice effect of this variant, resulting in partial retention of intron 9 that is expected to lead to a frameshift, premature truncation, and subsequent nonsense mediated decay (PMID: 32668095). However, some degree of normal splicing appears to be retained (PVS1_Strong_RNA). This variant has been detected in trans with a pathogenic variant in at least one individual with limb girdle muscular dystrophy (c.1194-9A>G, 1.0 pt, PMID: 30564623; LOVD Individual #00222031; ClinVar SCV004285915.1 internal data communication) (PM3, PP4). The highest minor allele frequency of this variant is 0.000001697 in the European (non-Finnish) population in gnomAD v4.1.0 (2/1178556 genome chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (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 1.0.0; 04/22/2025): PVS1_Strong_RNA, PM3, PP4, PM2_Supporting.

Met criteria codes

PP4	✔	At least one patient with this variant was clinically suspected to have limb girdle muscular dystrophy (PP4).
PVS1_Strong	✔	The NM_000070.3: c.1187A>G variant is CAPN3 is a missense variant predicted to cause substitution of glutamic acid by glycine at amino acid 396, p.(Glu396Gly). This variant affects the seventh nucleotide from the boundary of exon and intron 9 and has a SpliceAI score of 0.09 for gain of an alternative donor site in intron 9. Minigene assays have demonstrated a splice effect of this variant, resulting in partial retention of intron 9 that is expected to lead to a frameshift, premature truncation, and subsequent nonsense mediated decay (PMID: 32668095). However, some degree of normal splicing appears to be retained. (PVS1_Strong_RNA)
PM3	✔	This variant has been detected in trans with a pathogenic variant in at least one individual with limb girdle muscular dystrophy (c.1194-9A>G, 1.0 pt, PMID: 30564623; LOVD Individual #00222031; ClinVar SCV004285915.1 internal data communication) (PM3).
PM2_Supporting	✔	The highest minor allele frequency of this variant is 0.000001697 in the European (non-Finnish) population in gnomAD v4.1.0 (2/1178556 genome chromosomes), which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.93, which is above the threshold of 0.7, evidence that correlates with impact to CAPN3 function; however, minigene assays suggest this variant affects splicing, and PVS1_RNA was applied (PP3 not applicable).

PM5		✖	c.1187A>T p.(Glu396Val) not in ClinVar affects 7th nucleotide (3rd residue) from intron/exon boundary, Splice AI 0.05, Minigene assay shows no impact on splicing. Revel 0.897 LOVD Individual #00289319: c.1187A>T reported as in trans with c.946-1G>A: not yet curated by VCEP but expected P; interpreted for LGMDR1 but no phenotype for individual c.1187A>Tseems unlikely to reach LP without PM5: at best PP3, PM3, PP4, PM2_Supporting. Also, would not apply PM5 if splicing is mechanism (but could be dual contribution of missense change and altered splicing to disease mechanism). no other variants affecting this codon seem to have been reported

Curation History

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