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Variant: NM_000070.3(CAPN3):c.1327T>C (p.Ser443Pro)

Version: 1.0

CA391999594

662490 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 298254f3-0fc8-4f28-9666-22d64a2702ae
Approved on: 2026/4/29
Published on: 2026/5/7

HGVS expressions

NM_000070.3:c.1327T>C
NM_000070.3(CAPN3):c.1327T>C (p.Ser443Pro)
NC_000015.10:g.42399625T>C
CM000677.2:g.42399625T>C
NC_000015.9:g.42691823T>C
CM000677.1:g.42691823T>C
NC_000015.8:g.40479115T>C
NG_008660.1:g.56523T>C
ENST00000349748.8:c.1183T>C
ENST00000357568.8:c.1327T>C
ENST00000397163.8:c.1327T>C
ENST00000466369.5:n.1836T>C
ENST00000483208.5:n.1558T>C
ENST00000495723.1:n.1558T>C
ENST00000549793.5:n.1558T>C
ENST00000638141.2:n.1198T>C
ENST00000673658.1:n.311T>C
ENST00000673705.1:c.282T>C
ENST00000318023.11:c.1183T>C
ENST00000349748.7:c.1183T>C
ENST00000357568.7:c.1327T>C
ENST00000397163.7:c.1327T>C
NM_000070.2:c.1327T>C
NM_024344.1:c.1327T>C
NM_173087.1:c.1183T>C
NM_024344.2:c.1327T>C
NM_173087.2:c.1183T>C

Likely Pathogenic

Met criteria codes 4

PP3 PP4_Moderate PM3_Strong PM2_Supporting

Not Met criteria codes 1

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 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.1327T>C variant in CAPN3 is a missense variant predicted to cause substitution of serine with proline at amino acid position 443, p.(Ser443Pro). This variant has been detected in at least six unrelated individuals with LGMD, where it was identified in unconfirmed phase with two unique pathogenic variants (c.1505T>C p.(Thr501Ile), 0.5 pts x3, PMID: 35135626, 26810512, 39258114; c.1746-20C>G, 0.5 pts x3, GRASP-LGMD Consortium, ClinVar SCV000960844.6 internal data communication) (PM3_Strong). At least one patient with this variant and a second CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 35135626, 26810512; PP4_Moderate). The Grpmax variant allele frequency in gnomAD v.4.1.1 is 0.000001698 in the European (non-Finnish) population (2/1177684 chromosomes) (PM2_Supporting). The computational predictor REVEL gives a score of 0.896, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). 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 (specifications v2.0.0; 04/29/2026): PM3_Strong, PP4_Moderate, PM2_Supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.896, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.00
PP4_Moderate	✔	At least one patient with this variant and a second CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 35135626, 26810512; PP4_Moderate).
PM3_Strong	✔	This variant has been detected in at least six unrelated individuals with LGMD, where it was identified in unconfirmed phase with two unique pathogenic variants (c.1505T>C p.(Thr501Ile), 0.5 pts x3, PMID: 35135626, 26810512, 39258114; c.1746-20C>G, 0.5 pts x3, GRASP-LGMD Consortium, ClinVar SCV000960844.6 internal data communication) (PM3_Strong). Note: This variant is absent from gnomAD v2 so we cannot evaluate co-occurrence with c.1746-20C>G and c.1505T>C (p.Ile502Thr).
PM2_Supporting	✔	The Grpmax variant allele frequency in gnomAD v.4.1.1 is 0.000001698 in the European (non-Finnish) population (2/1177684 chromosomes) (PM2_Supporting).

Not Met criteria codes

PM5	✖	This variant is a novel missense change at an amino acid residue where a different missense change determined to be likely pathogenic has been seen before in one patient with LGMD2A, muscle biopsy with dystrophic changes and severe reduction in calpain expression. Genetic analysis showing compound heterozygosity for a likely pathogenic missense variant c.1328C>T p.(Ser443Phe) and pathogenic variant c.1746-20C>G PMID 33386810. PMID 22926650: single het case. PMID 31127727: unknown phase with c.1746-20C>G. c.1328C>T p.(Ser443Phe) looks likely to be classified as likely pathogenic (assume PM2_Supporting, assume PP3, 1.5 PM3 pts (PM3: PMID: 33386810, 31127727), PP4_Moderate), which would enable PP5_Supporting, but that would not upgrade the classification of

this variant, so at this time we opted not to formally curate c.1328C>T p.(Ser443Phe). additional citations in LOVD CAPN3_000351

Curation History

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