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Variant: NM_000070.3(CAPN3):c.363C>G (p.Ile121Met)

Version: 1.0

CA269832799

496977 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 76086dfa-1281-4bf9-8018-b573803698aa
Approved on: 2025-01-07
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HGVS expressions

NM_000070.3:c.363C>G
NM_000070.3(CAPN3):c.363C>G (p.Ile121Met)
NC_000015.10:g.42384536C>G
CM000677.2:g.42384536C>G
NC_000015.9:g.42676734C>G
CM000677.1:g.42676734C>G
NC_000015.8:g.40464026C>G
NG_008660.1:g.41434C>G
ENST00000349748.8:c.363C>G
ENST00000357568.8:c.363C>G
ENST00000397163.8:c.363C>G
ENST00000466369.5:n.594C>G
ENST00000483208.5:n.594C>G
ENST00000495723.1:n.594C>G
ENST00000549793.5:n.594C>G
ENST00000638141.2:n.378C>G
ENST00000673705.1:c.54C>G
ENST00000318023.11:c.363C>G
ENST00000349748.7:c.363C>G
ENST00000357568.7:c.363C>G
ENST00000397163.7:c.363C>G
NM_000070.2:c.363C>G
NM_024344.1:c.363C>G
NM_173087.1:c.363C>G
NM_024344.2:c.363C>G
NM_173087.2:c.363C>G

Likely Pathogenic

Met criteria codes 4

PM3_Strong PP3 PP4 PM2_Supporting

Not Met criteria codes 2

PM5 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.363C>G variant in CAPN3 is a missense variant predicted to cause substitution of isoleucine by methionine at amino acid 121 (p.Ile121Met). This variant has been detected in at least five individuals with LGMD (PMID: 230564623; LOVD CAPN3_000401; ClinVar SCV003459936.1 internal data communication). In at least three of these patients, the variant was identified in unknown phase with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 1.0 pt; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts), and in one patient it was confirmed in trans with a pathogenic variant (c.146G>A (p.Arg49His), 1.0 pt) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PMID: 230564623; LOVD Individual #00213632) (PP4). The highest population minor allele frequency in gnomAD v3.1.2 is 0.00002412 (1/41464 African/African American genome alleles), which is lower than the LGMD VECP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.89, which is above the 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 (LGMD VCEP specifications version 1.0.0; 01/07/2025): PM3_Strong, PP4, PM2_Supporting, PP3.

Met criteria codes

PM3_Strong	✔	This variant has been detected in at least five individuals with LGMD (PMID: 230564623; LOVD CAPN3_000401; SCV003459936.1). In at least three of these patients, the variant was identified in unknown phase with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 1.0 pt; c.2362_2363delinsTCATCT p.(Arg788Serfs*14), 0.5 pts), and in one patient it was confirmed in trans with a pathogenic variant (c.146G>A (p.Arg49His), 1.0 pt) (PM3_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.89, which is above the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3).
PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PMID: 230564623; LOVD CAPN3_000401) (PP4).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v3.1.2 is 0.00002412 (1/41464 African/African American genome alleles), which is lower than the ClinGen LGMD VECP threshold (≤0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5	✖	c.361A>G (p.Ile121Val) is VUS in ClinVar by 1 submitter with no citations
PVS1	✖	No impact on splicing in a minigene assay (but not in a splice region, spliceAI 0.05)

Curation History

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