

Variant: *NM_000070.3(CAPN3):c.865C>T (p.Arg289Trp)*

Version: 1.0

CA7511150 [↗](#)

282646 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: a0d4d521-e795-49ca-ac87-66979fe747d8

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HGVS expressions

NM_000070.3(CAPN3):c.865C>T (p.Arg289Trp)

NM_000070.3:c.865C>T

NC_000015.10:g.42390016C>T

CM000677.2:g.42390016C>T

NC_000015.9:g.42682214C>T

CM000677.1:g.42682214C>T

NC_000015.8:g.40469506C>T

NG_008660.1:g.46914C>T

ENST00000349748.8:c.801+920C>T

ENST00000357568.8:c.865C>T

ENST00000397163.8:c.865C>T

ENST00000466369.5:n.1374C>T

ENST00000483208.5:n.1096C>T

ENST00000495723.1:n.1096C>T

ENST00000549793.5:n.1096C>T

ENST00000638141.2:n.816+920C>T

ENST00000673705.1:c.70+5464C>T

ENST00000318023.11:c.801+920C>T

ENST00000349748.7:c.801+920C>T

ENST00000357568.7:c.865C>T

ENST00000397163.7:c.865C>T

NM_000070.2:c.865C>T

NM_024344.1:c.865C>T

NM_173087.1:c.801+920C>T

NM_024344.2:c.865C>T

NM_173087.2:c.801+920C>T

Likely Pathogenic

Met criteria codes **2**

PP4_Moderate

PM3_Strong

Not Met criteria codes **2**

PP3

PM2

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 2.0.0

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.865C>T variant in CAPN3 is a missense variant expected to cause substitution of arginine with tryptophan at amino acid position 289 (p.Arg289Trp). The variant has been detected in at least 5 patients with LGMD (PMID: 7236769, 18337726, 37526466, 33505349, 30919934), including confirmed in trans with a pathogenic variant in two patients (c.1981del p.(Ile661Ter), 1.0 pts x2) and in unknown phase with a pathogenic variant in two patients (c.550del, 0.5 pts x2) (PM3_Strong). At least one patient with this variant and a second CAPN3 variant displayed progressive limb girdle muscle weakness and severely reduced expression of calpain-3 protein in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 18337726; PP4_Moderate). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.0001579 in gnomAD v4.1.1 (6/74992 African/ African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_supporting (≤ 0.0001) (PM2_Supporting not met). The computational predictor Revel gives a score of 0.52, which is below the threshold of 0.70 (PP3 not met). 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.

Met criteria codes

PP4_Moderate			At least one patient with this variant and a second CAPN3 variant displayed progressive limb girdle muscle weakness and severely reduced expression of calpain-3 protein in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 18337726; PP4_Moderate).
PM3_Strong			The variant has been detected in at least 5 patients with LGMD (PMID: 7236769, 18337726, 37526466, 33505349, 30919934), including confirmed in trans with a pathogenic variant in two patients (c.1981del p.(Ile661Ter), 1.0 pts x2) and in unknown phase with a pathogenic variant in two patients (c.550del, 0.5 pts x2) (PM3_Strong).

Not Met criteria codes

PP3			The computational predictor Revel gives a score of 0.52, which is below the threshold of 0.70 (PP3 not met). SpliceAI: 0.00
PM2			The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.0001579 in gnomAD v4.1.1 (6/74992 African/ African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold for PM2_supporting (≤ 0.0001) (PM2_Supporting not met).

Curation History [↗](#)

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