

Variant: NM_000070.3(CAPN3):c.2105C>T (p.Ala702Val)

Version: 1.0

CA10604398 [↗](#)

283099 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6f6669bf-fd07-4ba8-9c06-cc26ea482931

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HGVS expressions

NM_000070.3(CAPN3):c.2105C>T (p.Ala702Val)

- NM_000070.3:c.2105C>T
- NC_000015.10:g.42409985C>T
- CM000677.2:g.42409985C>T
- NC_000015.9:g.42702183C>T
- CM000677.1:g.42702183C>T
- NC_000015.8:g.40489475C>T
- NG_008660.1:g.66883C>T
- ENST00000337571.9:c.110C>T
- ENST00000349748.8:c.1829C>T
- ENST00000357568.8:c.2087C>T
- ENST00000397163.8:c.2105C>T
- ENST00000397204.9:c.110C>T
- ENST00000466222.7:n.370C>T
- ENST00000466369.5:n.2596C>T
- ENST00000495723.1:n.2976C>T
- ENST00000549793.5:n.2318C>T
- ENST00000562199.2:c.113C>T
- ENST00000569136.6:c.110C>T
- ENST00000638141.2:n.1844C>T
- ENST00000673646.1:c.669C>T
- ENST00000673687.1:n.182C>T
- ENST00000673692.1:c.110C>T
- ENST00000673705.1:c.500C>T
- ENST00000673743.1:c.8C>T
- ENST00000673750.1:c.110C>T
- ENST00000673771.1:c.110C>T
- ENST00000673774.1:n.806C>T
- ENST00000673839.1:c.110C>T
- ENST00000673851.1:c.110C>T
- ENST00000673854.1:n.5527C>T
- ENST00000673886.1:c.110C>T
- ENST00000673890.1:c.110C>T
- ENST00000673893.1:c.29C>T
- ENST00000673928.1:c.110C>T
- ENST00000673936.1:c.110C>T
- ENST00000673939.1:c.110C>T

	ENST00000673950.1:n.379C>T ENST00000673978.1:c.248C>T ENST00000673987.1:c.110C>T ENST00000674011.1:c.110C>T ENST00000674018.1:c.110C>T ENST00000674027.1:n.165C>T ENST00000674041.1:c.110C>T ENST00000674052.1:c.329C>T ENST00000674093.1:c.110C>T ENST00000674119.1:c.110C>T ENST00000674130.1:n.323C>T ENST00000674135.1:c.287C>T ENST00000674139.1:c.110C>T ENST00000674146.1:c.110C>T ENST00000674149.1:c.110C>T ENST00000318023.11:c.1961C>T ENST00000337571.8:c.110C>T ENST00000349748.7:c.1829C>T ENST00000356316.7:c.110C>T ENST00000357568.7:c.2087C>T ENST00000397163.7:c.2105C>T ENST00000397200.8:c.569C>T ENST00000397204.8:c.110C>T ENST00000466222.6:n.1028C>T ENST00000561817.5:c.110C>T ENST00000562199.1:n.113C>T ENST00000564503.5:c.202C>T ENST00000565274.5:c.317C>T ENST00000565559.5:c.287C>T ENST00000569136.5:c.110C>T ENST00000569827.5:c.437C>T NM_000070.2:c.2105C>T NM_024344.1:c.2087C>T NM_173087.1:c.1829C>T NM_173088.1:c.569C>T NM_173089.1:c.110C>T NM_173090.1:c.110C>T NM_024344.2:c.2087C>T NM_173087.2:c.1829C>T NM_173088.2:c.569C>T NM_173089.2:c.110C>T NM_173090.2:c.110C>T
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Pathogenic

Met criteria codes 4

- PP4_Strong
- PP3
- PM3_Very Strong
- PM2_Supporting

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

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.2105C>T variant in CAPN3 is a missense variant expected to result in the substitution of alanine with valine at amino acid 702, p.(Ala702Val). This variant has been detected in at least 11 individuals with features consistent with LGMD (PMID: 19556129; 31937337; 35741838; 16141003; 27066573; 16650086; ClinVar SCV001218172.5 internal data communication). Five seemingly unrelated patients were homozygous, with familial consanguinity reported in four (0.25 pts x4, 0.5 pts x1, capped at 1.0 pt). Two patients had a likely pathogenic or pathogenic CAPN3 variant confirmed in trans (c.1993-1G>A, 1.0 pt, ClinVar SCV001218172.5 internal data communication; c.1981del p.(Gln660_Ile661insTer), 1.0 pt, PMID: 19556129), and two patients had a pathogenic variant in unknown phase (c.2120A>G (p.Asp707Gly), 0.5 pts, PMID: 27066573; c.2362_2363delinsTCATCT (p.Arg788SerfsTer14), 0.5 pts, PMID: 35741838) (PM3_Very Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 19556129) (PP4_Strong). The filtering allele frequency of this variant is 0.000011828 in gnomAD v4.1.0 exomes (the upper bound of the 95% confidence interval of 7/1111640 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.77, 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 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; 05/14/2025): PM3_Very Strong, PP4_Strong, PP3, PM2_Supporting.

Met criteria codes

PP4_Strong			At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and absent expression of calpain-3 protein in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 19556129) (PP4_Strong).
PP3			The computational predictor REVEL gives a score of 0.77, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function.
PM3_Very Strong			This variant has been detected in at least 11 individuals with features consistent with LGMD (PMID: 19556129; 31937337; 35741838; 16141003; 27066573; 16650086; ClinVar SCV001218172.5 internal data communication). Five seemingly unrelated patients were homozygous, with familial consanguinity reported in four (0.25 x4, 0.5 x1, capped at 1.0 pt). Two patients had a likely pathogenic or pathogenic CAPN3 variant confirmed in trans (c.1993-1G>A, 1.0 pt, ClinVar SCV001218172.5 internal data communication; c.1981del p.(Gln660_Ile661insTer), 1.0 pt, PMID: 19556129), and two patients had a pathogenic variant in unknown phase (c.2120A>G (p.Asp707Gly), 0.5 pts, PMID: 27066573; c.2362_2363delinsTCATCT (p.Arg788SerfsTer14), 0.5 pts, PMID: 35741838) (PM3_Very Strong). confirmed neither variant in unknown phase predicted to be on same haplotype classification of c.2120A>G (p.Asp707Gly) as P is pending approval as BS1 exception; will be presented at April 22 2025 VCEP call
PM2_Supporting			The filtering allele frequency of this variant is 0.000011828 in gnomAD v4.1.0 exomes (the upper bound of the 95% confidence interval for 7/1111640 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold (< 0.0001) for PM2_Supporting, meeting this criterion.

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