

Variant: NM_000070.3(CAPN3):c.2288A>G (p.Tyr763Cys)

Version: 1.0

CA7511820 [↗](#)

282681 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a5e60904-d166-4765-b611-613a00f60508

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HGVS expressions

NM_000070.3(CAPN3):c.2288A>G (p.Tyr763Cys)

- NM_000070.3:c.2288A>G
- NC_000015.10:g.42410908A>G
- CM000677.2:g.42410908A>G
- NC_000015.9:g.42703106A>G
- CM000677.1:g.42703106A>G
- NC_000015.8:g.40490398A>G
- NG_008660.1:g.67806A>G
- ENST00000337571.9:c.293A>G
- ENST00000349748.8:c.2012A>G
- ENST00000357568.8:c.2270A>G
- ENST00000397163.8:c.2288A>G
- ENST00000397204.9:c.293A>G
- ENST00000466222.7:n.733A>G
- ENST00000466369.5:n.2779A>G
- ENST00000495723.1:n.3159A>G
- ENST00000549793.5:n.2501A>G
- ENST00000562199.2:c.292A>G
- ENST00000567817.6:c.77A>G
- ENST00000568153.2:c.154A>G
- ENST00000569136.6:c.293A>G
- ENST00000638141.2:n.2027A>G
- ENST00000673646.1:c.852A>G
- ENST00000673684.1:n.270A>G
- ENST00000673692.1:c.293A>G
- ENST00000673705.1:c.831A>G
- ENST00000673743.1:c.191A>G
- ENST00000673750.1:c.293A>G
- ENST00000673771.1:c.293A>G
- ENST00000673774.1:n.1421A>G
- ENST00000673839.1:c.293A>G
- ENST00000673851.1:c.293A>G
- ENST00000673854.1:n.5710A>G
- ENST00000673886.1:c.293A>G
- ENST00000673890.1:c.293A>G
- ENST00000673928.1:c.293A>G
- ENST00000673936.1:c.293A>G

ENST00000673939.1:c.*82A>G
ENST00000673950.1:n.562A>G
ENST00000673978.1:c.431A>G
ENST00000673987.1:c.*82A>G
ENST00000674011.1:c.*82A>G
ENST00000674018.1:c.293A>G
ENST00000674027.1:n.439A>G
ENST00000674041.1:c.293A>G
ENST00000674052.1:c.512A>G
ENST00000674093.1:c.293A>G
ENST00000674119.1:c.293A>G
ENST00000674135.1:c.470A>G
ENST00000674139.1:c.293A>G
ENST00000674146.1:c.293A>G
ENST00000674149.1:c.293A>G
ENST00000318023.11:c.2144A>G
ENST00000337571.8:c.293A>G
ENST00000349748.7:c.2012A>G
ENST00000356316.7:c.293A>G
ENST00000357568.7:c.2270A>G
ENST00000397163.7:c.2288A>G
ENST00000397200.8:c.752A>G
ENST00000397204.8:c.293A>G
ENST00000466222.6:n.1211A>G
ENST00000561817.5:c.293A>G
ENST00000562199.1:n.292A>G
ENST00000564503.5:c.331A>G
ENST00000565274.5:c.466A>G
ENST00000565559.5:c.470A>G
ENST00000567817.5:c.104A>G
ENST00000568153.1:c.25A>G
ENST00000569136.5:c.293A>G
ENST00000569827.5:c.620A>G
NM_000070.2:c.2288A>G
NM_024344.1:c.2270A>G
NM_173087.1:c.2012A>G
NM_173088.1:c.752A>G
NM_173089.1:c.293A>G
NM_173090.1:c.293A>G
NM_024344.2:c.2270A>G
NM_173087.2:c.2012A>G
NM_173088.2:c.752A>G
NM_173089.2:c.293A>G
NM_173090.2:c.293A>G

Pathogenic

Met criteria codes 4

- PM2_Supporting
- PP4_Strong
- PP3
- PM3_Strong

Evidence Links 0

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_213599.3: c.2288A>G variant in CAPN3 is a missense variant expected to cause the substitution of tyrosine with cysteine at position 763, p.(Tyr763Cys). This variant has been identified in at least six individuals with features consistent with LGMD (PMID: 16816913, 32994280, 33963534, 30564623; LOVD CAPN3_000119), including in a homozygous state without reported consanguinity in two unrelated patients (1.0 pt; PMID: 33963534, 30564623; LOVD Individuals #00361984, #00220100). It has also been reported in unconfirmed phase with a pathogenic variant in two patients (c.1621C>T p.(Arg541Trp), 0.5 pts, PMID: 32994280, LOVD Individual #00311254; c.2243G>A p.(Arg748Gln), 0.5 pts, PMID: 30564623, LOVD Individual #00220339) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic CAPN3 allele had progressive pelvic girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 1681691; PP4_Strong). The upper bound of the 95% confidence interval (95% CI) of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000007757 (4/1179962 European (non-Finnish) chromosomes, which is less than the threshold of 0.0001 (PM2_Supporting). The computational predictor REVEL gives a score of 0.93, which exceeds the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 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 criteria applied, as specified by the LGMD VCEP (specifications version 2.0.0; 02/26/2026): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting			The upper bound of the 95% confidence interval (95% CI) of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000007757 (4/1179962 European (non-Finnish) chromosomes, which is less than the threshold of 0.0001 (PM2_Supporting).
PP4_Strong			At least one patient with this variant and a second presumed diagnostic CAPN3 allele had progressive pelvic girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 1681691; PP4_Strong).
PP3			The computational predictor REVEL gives a score of 0.93, which exceeds the VCEP threshold of ≥ 0.70 , evidence that correlates with impact to ANO5 function (PP3). SpliceAI: 0
PM3_Strong			This variant has been identified in at least six individuals with features consistent with LGMD (PMID: 16816913, 32994280, 33963534, 30564623; LOVD CAPN3_000119), including in a homozygous state without reported consanguinity in two unrelated patients (1.0 pt; PMID: 33963534, 30564623; LOVD Individuals #00361984, #00220100). It has also been reported in unconfirmed phase with a pathogenic variant in two patients (c.1621C>T p.(Arg541Trp), 0.5 pts, PMID: 32994280, LOVD Individual #00311254; c.2243G>A p.(Arg748Gln), 0.5 pts, PMID: 30564623, LOVD Individual #00220339) (PM3_Strong). unconfirmed phase: c.1621C>T p.(Arg541Trp): predicted on different haplotypes c.2243G>A p.(Arg748Gln): predicted on different haplotypes

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