

Variant: NM_000070.3(CAPN3):c.2120A>G (p.Asp707Gly)

CA7511744 [↗](#)

468648 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7f534c0d-0dbe-4d2e-88e2-88c804cde635

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Version: 1.0

HGVS expressions

NM_000070.3(CAPN3):c.2120A>G (p.Asp707Gly)

NM_000070.3:c.2120A>G

NC_000015.10:g.42410432A>G

CM000677.2:g.42410432A>G

NC_000015.9:g.42702630A>G

CM000677.1:g.42702630A>G

NC_000015.8:g.40489922A>G

NG_008660.1:g.67330A>G

ENST00000337571.9:c.125A>G

ENST00000349748.8:c.1844A>G

ENST00000357568.8:c.2102A>G

ENST00000397163.8:c.2120A>G

ENST00000397204.9:c.125A>G

ENST00000466222.7:n.385A>G

ENST00000466369.5:n.2611A>G

ENST00000495723.1:n.2991A>G

ENST00000549793.5:n.2333A>G

ENST00000562199.2:c.124A>G

ENST00000569136.6:c.125A>G

ENST00000638141.2:n.1859A>G

ENST00000673646.1:c.684A>G

ENST00000673684.1:n.102A>G

ENST00000673687.1:n.629A>G

ENST00000673692.1:c.125A>G

ENST00000673705.1:c.511-156A>G

ENST00000673743.1:c.23A>G

ENST00000673750.1:c.125A>G

ENST00000673771.1:c.125A>G

ENST00000673774.1:n.1253A>G

ENST00000673839.1:c.125A>G

ENST00000673851.1:c.125A>G

ENST00000673854.1:n.5542A>G

ENST00000673886.1:c.125A>G

ENST00000673890.1:c.125A>G

ENST00000673893.1:c.323A>G

ENST00000673928.1:c.125A>G

ENST00000673936.1:c.125A>G

	ENST00000673939.1:c.125A>G ENST00000673950.1:n.394A>G ENST00000673978.1:c.263A>G ENST00000673987.1:c.125A>G ENST00000674011.1:c.125A>G ENST00000674018.1:c.125A>G ENST00000674027.1:n.180A>G ENST00000674041.1:c.125A>G ENST00000674052.1:c.344A>G ENST00000674093.1:c.125A>G ENST00000674119.1:c.125A>G ENST00000674135.1:c.302A>G ENST00000674139.1:c.125A>G ENST00000674146.1:c.125A>G ENST00000674149.1:c.125A>G ENST00000318023.11:c.1976A>G ENST00000337571.8:c.125A>G ENST00000349748.7:c.1844A>G ENST00000356316.7:c.125A>G ENST00000357568.7:c.2102A>G ENST00000397163.7:c.2120A>G ENST00000397200.8:c.584A>G ENST00000397204.8:c.125A>G ENST00000466222.6:n.1043A>G ENST00000561817.5:c.125A>G ENST00000562199.1:n.124A>G ENST00000564503.5:c.217A>G ENST00000565274.5:c.352A>G ENST00000565559.5:c.302A>G ENST00000569136.5:c.125A>G ENST00000569827.5:c.452A>G NM_000070.2:c.2120A>G NM_024344.1:c.2102A>G NM_173087.1:c.1844A>G NM_173088.1:c.584A>G NM_173089.1:c.125A>G NM_173090.1:c.125A>G NM_024344.2:c.2102A>G NM_173087.2:c.1844A>G NM_173088.2:c.584A>G NM_173089.2:c.125A>G NM_173090.2:c.125A>G
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Pathogenic

Met criteria codes 4

- PP3
- PP4
- PP1_Strong
- PM3_Strong

Not Met criteria codes 2

- PM2
- BS1

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.2120A>G variant in CAPN3 is a missense variant predicted to cause substitution of asparagine with glycine at amino acid position 707, p.(Asp707Gly). This variant has been reported in over 20 patients with features of LGMD and is particularly common among patients with East Asian ancestry (PMID: 28403181, 17258832, 10567047, 19556129, 27066573, 37974208, 32994280, 33899113, 30127231, 39188286, 11525884; LOVD CAPN3_000118). These reports include at least five unrelated homozygous cases without reported familial consanguinity (1.0 pt; PMID: 17258832, 10567047, 32994280, 11525884) and at least one observation where the variant was confirmed in trans with a likely pathogenic or pathogenic variant (c.2201_2202del p.(Tyr734Ter), 1.0 pt, PMID: 33899113) (PM3_Strong). It has also been reported to segregate with the LGMD phenotype in six affected family members from four families (PP1_Strong; PMID: 37974208, 32994280, 39188286, 11525884). At least one patient with this variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 26632398, 19556129, 10567047, 17258832; PP4 (capped with PP1_Strong)). The filtering allele frequency in gnomAD v4.1.0 exomes is 0.001250 (the lower threshold of the 95% CI of 62/39700 East Asian chromosomes), which is above the LGMD VCEP threshold (0.001) for BS1. However, this variant is one of the most commonly described CAPN3 variants reported in patients in this population, and the VCEP opted not to apply this code (BS1 exception). The computational predictor REVEL gives a score of 0.966, 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; 04/22/2025): PM3_Strong, PP1_Strong, PP4, PP3.

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.966, which is above the LGMD VCEP threshold of ≥ 0.70 , evidence that correlates with impact to CAPN3 function (PP3).
PP4			At least two patients with this variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression, which is specific for CAPN3-related LGMD (PMID: 26632398, 19556129, 10567047, 17258832; PP4 (capped with PP1_Strong)).
PP1_Strong			The variant has been reported to segregate with the LGMD phenotype in six affected family members from four families (PP1_Strong; PMID 37974208, 32994280, 39188286, 11525884).
PM3_Strong			This variant has been reported in over 20 patients with features of LGMD and is particularly common among patients with East Asian ancestry (PMID: 28403181, 17258832, 10567047, 19556129, 27066573, 37974208, 32994280, 33899113, 30127231, 39188286, 11525884; LOVD CAPN3_000118). These reports include at least five unrelated homozygous cases without reported familial consanguinity (1.0 pt; PMID: 17258832, 10567047, 32994280, 11525884) and at least one observation where the variant was confirmed in trans with a likely pathogenic or pathogenic variant (c.2201_2202del p.(Tyr734Ter), 1.0 pt, PMID: 33899113) (PM3_Strong).

Not Met criteria codes

PM2			The filtering allele frequency (the upper threshold of the 95% CI of 62/39700 (exome chromosomes) is 0.001929 for the East Asian population in gnomAD v4.1.0, which is above the ClinGen LGMD VCEP threshold (< 0.0001) for
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PM2_Supporting, and therefore does not meet this criterion (PM2_Supporting not met).

BS1



The filtering allele frequency (the lower threshold of the 95% CI of 62/39700 (exome chromosomes) is 0.001929 for the East Asian population in gnomAD v4.1.0, which is above the ClinGen LGMD VCEP threshold (0.001) for BS1. However, this variant is one of the most commonly described CAPN3 variants reported in patients in this population, and the VCEP opted not to apply this code (BS1 exception).

Curation History [↗](#)

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