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Variant: NM_000070.3(CAPN3):c.2243G>A (p.Arg748Gln)

Version: 1.0

CA345536

128570 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: e621ac33-dbf3-42fe-b8c2-4a3287c347d1
Approved on: 2026/3/12
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HGVS expressions

NM_000070.3(CAPN3):c.2243G>A (p.Arg748Gln)
NM_000070.3:c.2243G>A
NC_000015.10:g.42410646G>A
CM000677.2:g.42410646G>A
NC_000015.9:g.42702844G>A
CM000677.1:g.42702844G>A
NC_000015.8:g.40490136G>A
NG_008660.1:g.67544G>A
ENST00000337571.9:c.248G>A
ENST00000349748.8:c.1967G>A
ENST00000357568.8:c.2225G>A
ENST00000397163.8:c.2243G>A
ENST00000397204.9:c.248G>A
ENST00000466222.7:n.599G>A
ENST00000466369.5:n.2734G>A
ENST00000495723.1:n.3114G>A
ENST00000549793.5:n.2456G>A
ENST00000562199.2:c.247G>A
ENST00000567817.6:c.32G>A
ENST00000568153.2:c.109G>A
ENST00000569136.6:c.248G>A
ENST00000638141.2:n.1982G>A
ENST00000673646.1:c.807G>A
ENST00000673684.1:n.225G>A
ENST00000673687.1:n.843G>A
ENST00000673692.1:c.248G>A
ENST00000673705.1:c.569G>A
ENST00000673743.1:c.146G>A
ENST00000673750.1:c.248G>A
ENST00000673771.1:c.248G>A
ENST00000673774.1:n.1376G>A
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ENST00000673854.1:n.5665G>A
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ENST00000673978.1:c.386G>A
ENST00000673987.1:c.248G>A
ENST00000674011.1:c.248G>A
ENST00000674018.1:c.248G>A
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ENST00000674052.1:c.467G>A
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ENST00000674119.1:c.248G>A
ENST00000674135.1:c.425G>A
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ENST00000674146.1:c.248G>A
ENST00000674149.1:c.248G>A
ENST00000318023.11:c.2099G>A
ENST00000337571.8:c.248G>A
ENST00000349748.7:c.1967G>A
ENST00000356316.7:c.248G>A
ENST00000357568.7:c.2225G>A
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ENST00000397200.8:c.707G>A
ENST00000397204.8:c.248G>A
ENST00000466222.6:n.1166G>A
ENST00000561817.5:c.248G>A
ENST00000562199.1:n.247G>A
ENST00000564503.5:c.286G>A
ENST00000565274.5:c.421G>A
ENST00000565559.5:c.425G>A
ENST00000567817.5:c.59G>A
ENST00000569136.5:c.248G>A
ENST00000569827.5:c.575G>A
NM_000070.2:c.2243G>A
NM_024344.1:c.2225G>A
NM_173087.1:c.1967G>A
NM_173088.1:c.707G>A
NM_173089.1:c.248G>A
NM_173090.1:c.248G>A
NM_024344.2:c.2225G>A
NM_173087.2:c.1967G>A
NM_173088.2:c.707G>A
NM_173089.2:c.248G>A
NM_173090.2:c.248G>A

Pathogenic

Met criteria codes 4

PP4_Strong PP1 PP3 PM3_Strong

Not Met criteria codes 2

PM2 BP7

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specification: *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CAPN3 Version 2.0.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.2243G>A variant in CAPN3 is a missense variant expected to result in the substitution of arginine with glutamine at amino acid 748, p.(Arg748Gln). Across a selection of the available literature, this variant has been reported in at least 16 individuals with features consistent with LGMD (PMID: 32994280, 22443334, 15689361, 30838351; LOVD CAPN3_000028), including in a homozygous state without reported consanguinity in at least six unrelated patients of Chinese, Turkish, and Spanish ancestry (1.0 pt; PMID: 32994280, 22443334, 15689361, 30838351). It has also been identified in unconfirmed phase with a pathogenic variant in at least two patients (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 32994280, LOVD Individual #00311286; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, PMID: 15689361, LOVD Individual #00214354) (PM3_Strong). This variant was identified in a homozygous state in one individual with both progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 22443334; PP4_Strong). In addition, this variant has also been shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 30838351; PP1). The upper bound of the 95% confidence interval (95% CI) of the highest population variant allele frequency in gnomAD v4.1.0 is 0.0002408 (8/59942 Admixed American chromosomes), which is higher than the threshold of 0.0001 (PM2_Supporting not met). This variant had no effect on splicing in a mini-gene assay (PMID: 32668095), but a deleterious effect of the amino acid change cannot be excluded (BP7_Strong not met), and the computational predictor REVEL gives a score of 0.724, 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 2.0.0; 03/12/2026): PM3_Strong, PP4_Strong, PP1, PP3.

Met criteria codes

PP4_Strong	✔	This variant has been identified in a homozygous state in one individual with both progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 22443334; PP4_Strong).
PP1	✔	This variant has also been shown to co-segregate with autosomal recessive LGMD in one affected family member (PMID: 30838351; PP1).
PP3	✔	The computational predictor REVEL gives a score of 0.724, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI 0.01
PM3_Strong	✔	Across a selection of the available literature, this variant has been reported in at least 16 individuals with features consistent with LGMD (PMID: 32994280, 22443334, 15689361, 30838351; LOVD CAPN3_000028), including in a homozygous state without reported consanguinity in at least six unrelated patients of Chinese, Turkish, and Spanish ancestry (1.0 pt; PMID: 32994280, 22443334, 15689361, 30838351). It has also been identified in unconfirmed phase with a pathogenic variant in at least two patients (c.2120A>G p.(Asp707Gly), 0.5 pts, PMID: 32994280, LOVD Individual #00311286; c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, PMID: 15689361, LOVD Individual #00214354) (PM3_Strong). variants in unconfirmed phase: c.2120A>G p.(Asp707Gly) - predicted on different haplotypes c.2362_2363delinsTCATCT p.(Arg788SerfsTer14) - absent from gnomAD, cannot assess co-occurrence prediction

Not Met criteria codes

PM2	✖	The upper bound of the 95% confidence interval (95% CI) of the highest population variant allele frequency in gnomAD v4.1.0 is 0.0002408 (8/59942 Admixed American chromosomes), which is higher than the threshold of 0.0001 (PM2_Supporting not met).
BP7	✖	This variant had no effect on splicing in a mini-gene assay (PMID: 32668095), but a deleterious effect of the amino acid change cannot be excluded (BP7_Strong not met).

Curation History

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