The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000070.3(CAPN3):c.1435A>G (p.Ser479Gly)

Version: 1.0

CA220341

92405 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6a95fd1b-624a-4eee-bcfa-a8b7670b0549
Approved on: 2026/2/26
Published on: 2026/4/9

HGVS expressions

NM_000070.3(CAPN3):c.1435A>G (p.Ser479Gly)
NM_000070.3:c.1435A>G
NC_000015.10:g.42401721A>G
CM000677.2:g.42401721A>G
NC_000015.9:g.42693919A>G
CM000677.1:g.42693919A>G
NC_000015.8:g.40481211A>G
NG_008660.1:g.58619A>G
ENST00000349748.8:c.1291A>G
ENST00000357568.8:c.1435A>G
ENST00000397163.8:c.1435A>G
ENST00000466369.5:n.1944A>G
ENST00000483208.5:n.1666A>G
ENST00000495723.1:n.1666A>G
ENST00000549793.5:n.1666A>G
ENST00000638141.2:n.1306A>G
ENST00000673705.1:c.309+2069A>G
ENST00000318023.11:c.1291A>G
ENST00000349748.7:c.1291A>G
ENST00000357568.7:c.1435A>G
ENST00000397163.7:c.1435A>G
NM_000070.2:c.1435A>G
NM_024344.1:c.1435A>G
NM_173087.1:c.1291A>G
NM_024344.2:c.1435A>G
NM_173087.2:c.1291A>G

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP4_Strong | PP3

Not Met criteria codes 15

PM5 | PM4 | PM2 | BA1 | BS1 | BS4 | BS3 | BP7 | BP4 | BP3 | BP2 | PVS1 | PS1 | PS3 | PP1

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 Links 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.1435A>G variant in CAPN3 is a missense variant predicted to cause the substitution of serine to glycine at codon 479, p.(Ser479Gly). This variant has been identified in at least 10 individuals with features consistent with LGMD (PMID: 32896923, 27055500, 27066573, 18563459, 30564623, 18055493, 15689361, 11297944, 11166169, 10330340), including in a homozygous state without reported consanguinity in three unrelated patients (1.0 pt, PMID: 18055493, 30564623; LOVD Individuals #00214581, #00214598, #00222203) and confirmed in trans with a likely pathogenic or pathogenic variant in one patient (c.1706T>C p.(Phe569Ser), 1.0 pt, PMID: 32896923). It has also been reported in unconfirmed phase with a pathogenic variant in four patients (c.550del, p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00222487; c.327_328dup, p.(Arg110ProfsTer18), 0.5 pts, PMID: 18055493, LOVD Individual #00214565; c.1743_1744del, p.(Glu582GlyfsTer3), 0.5 pts, PMID: 30564623, LOVD Individual #00219474; c.258dup, p.(Leu87SerfsTer4), 0.5 pts, PMID: 30564623, LOVD Individual #00220962) (PM3_Very strong). At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 18055493; PP4_Strong). The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0001347 in the European (non-Finnish) population (159/1180030 chromosomes), which is higher than the VCEP threshold for PM2_Supporting (<0.0001) (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.887, 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; 02/26/2026): PM3_Very strong, PP4_Strong, PP3.

Met criteria codes

PM3_Very Strong	✔	This variant has been identified in at least 10 individuals with features consistent with LGMD (PMID: 32896923, 27055500, 27066573, 18563459, 30564623, 18055493, 15689361, 11297944, 11166169, 10330340), including in a homozygous state without reported consanguinity in three unrelated patients (1.0 pt, PMID: 18055493, 30564623; LOVD Individuals #00214581, #00214598, #00222203) and confirmed in trans with a likely pathogenic or pathogenic variant in one patient (c.1706T>C p.(Phe569Ser), 1.0 pt, PMID: 32896923). It has also been reported in unconfirmed phase with a pathogenic variant in four patients (c.550del, p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30564623, LOVD Individual #00222487; c.327_328dup, p.(Arg110ProfsTer18), 0.5 pts, PMID: 18055493, LOVD Individual #00214565; c.1743_1744del, p.(Glu582GlyfsTer3), 0.5 pts, PMID: 30564623, LOVD Individual #00219474; c.258dup, p.(Leu87SerfsTer4), 0.5 pts, PMID: 30564623, LOVD Individual #00220962) (PM3_Very strong). Scored cases: 4 pts PMID: 32896923 González-Mera 2020, LOVD #00313640 Confirmed in trans, c.1706T>C, p.(Phe569Ser), (independently at least LP, 1 pt). c.1706T>C, p.(Phe569Ser) is a proposed dominant variant, but this compound het patient had a more severe phenotype than the heterozygous family members. PubMed: Nallamilli 2018, LOVD #00222487 Heterozygous, phase unknown, c.550del, p.(Thr184Argfs*36), (independently curated as P by LGMD VCEP, Pathogenic, 0.5 pt). predicted on different haplotypes. PMID: 18055493 Groen 2007, LOVD #00214565 Heterozygous, phase unknown, c.327_328dup, p.(Arg110Profs*18), (independently curated as P by LGMD VCEP, 0.5 pt). not in gnomAD v2 exomes, so co-occurrence prediction not available. PMID: 30564623 Nallamilli 2018, LOVD #00219474 Heterozygous, phase unknown, c.1743_1744del, p.(Glu582Glyfs*3), (independently curated as P by LGMD VCEP, 0.5 pt). not in gnomAD v2, so co-occurrence prediction not available. PMID: 30564623 Nallamilli 2018, LOVD #00220962 Heterozygous, phase unknown, c.258dup, p.(Leu87Serfs*4), (curated by LGMD VCEP at P, 0.5 pt), predicted on a different haplotype PMID: 18055493 Groen 2007, LOVD #00214581 homozygous, 0.5 pts PMID: 18055493 Groen 2007, LOVD #00214598 homozygous, 0.5 pts PMID: 30564623 Nallamilli 2018, LOVD #00222203 homozygous, 0pt (max reached) Unscored cases: PMID: 27066573 Izumi 2015, LOVD #00265573 Confirmed in trans, c.1786A>T, p.K596Ter, Independently provisionally classified as at least LP (PVS1, PM2_Supporting) but question about possible splice effect. If we reduce the weight of PVS1, this variant will independently be a VUS and

can only contribute 0.25 pts. PMID: 10330340 Richard 1999, LOVD #00213956 Genotype not reported. PMID: 11297944 Pollitt 2001, LOVD #00213957 single hit PMID: 15689361 Sáenz 2005, LOVD #00213958 single hit LOVD #00213959 Genotype not reported. PMID: 18563459 Blázquez 2008 Heterozygous, phase unknown, c.1992 + 1G>T (p.Asp665LeufsX18), Intron 17, Splice Site, (not yet curated, at best 0.5 pt)

PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 allele displayed progressive limb girdle muscle weakness and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN2-related LGMD (PMID: 18055493; PP4_Strong).
PP3	✔	The computational predictor REVEL gives a score of 0.887, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3_met).

Not Met criteria codes

PM5	✖	No other missense at p.479 curated as LP/P.
PM4	✖	No in-frame deletions/insertions.
PM2	✖	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0001347 in the European (non-Finnish) population (159/1180030 chromosomes), which is higher than the VCEP threshold for PM2_Supporting (<0.0001) (PM2_Supporting not met).
BA1	✖	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0001347 in the European (non-Finnish) population (159/1180030 chromosomes), which is lower than the VCEP threshold for BA1_Stand-alone (>0.003) (BA1_Stand-alone not met).
BS1	✖	The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.0001347 in the European (non-Finnish) population (159/1180030 chromosomes), which is lower than the VCEP threshold for BS1_Strong (>0.001) (BS1_Strong not met).
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	To our knowledge, functional assays have not been reported for this variant.
BP7	✖	Not a synonymous variant.
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3	✖	No in-frame deletions/insertions.
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PVS1		✖	missense variant
PS1		✖	No other missense at p.479 curated as LP/P.
PS3		✖	To our knowledge, functional assays have not been reported for this variant.
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.