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Variant: NM_000070.3(CAPN3):c.1466G>A (p.Arg489Gln)

Version: 1.0

CA7511363

289644 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0b0ac82a-7ce7-4597-a9b6-24b3442c5dd5
Approved on: 2026/4/1
Published on: 2026/5/7

HGVS expressions

NM_000070.3(CAPN3):c.1466G>A (p.Arg489Gln)
NM_000070.3:c.1466G>A
NC_000015.10:g.42401752G>A
CM000677.2:g.42401752G>A
NC_000015.9:g.42693950G>A
CM000677.1:g.42693950G>A
NC_000015.8:g.40481242G>A
NG_008660.1:g.58650G>A
ENST00000349748.8:c.1322G>A
ENST00000357568.8:c.1466G>A
ENST00000397163.8:c.1466G>A
ENST00000466369.5:n.1975G>A
ENST00000483208.5:n.1697G>A
ENST00000495723.1:n.1697G>A
ENST00000549793.5:n.1697G>A
ENST00000638141.2:n.1337G>A
ENST00000673705.1:c.309+2100G>A
ENST00000318023.11:c.1322G>A
ENST00000349748.7:c.1322G>A
ENST00000357568.7:c.1466G>A
ENST00000397163.7:c.1466G>A
NM_000070.2:c.1466G>A
NM_024344.1:c.1466G>A
NM_173087.1:c.1322G>A
NM_024344.2:c.1466G>A
NM_173087.2:c.1322G>A

Pathogenic

Met criteria codes 3

PM3_Very Strong | PP4_Moderate | PP3

Not Met criteria codes 3

PM5 | PM2 | PVS1

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 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.1466G>A variant in CAPN3 is a missense variant expected to cause the substitution of arginine with glutamine at position 489, p.(Arg489Gln). This variant has been identified in at least 8 individuals with features consistent with LGMD (PMID: 30989743, 10484770, 30564623, 17994539; LOVD CAPN3_000018; ClinVar SCV000645479.8 internal data communication), including confirmed in trans with a likely pathogenic or pathogenic variant in one case with LGMD (c.1711del p.(Leu571SerfsTer23), 1.0 pt, PMID: 17994539, 26404900), one case with hyperCKemia (c.1469G>A p.(Arg490Gln), 1.0 pt, PMID: 18854869, 14578192), and one case with chronic proximal muscle weakness (c.1715G>A (p.Arg572Gln), 1.0 pt, ClinVar SCV000645479.8 internal data communication). It has also been reported in unknown phase with a pathogenic variant in at least two patients (c.2182C>T p.(Gln728Ter), 0.5 pts, PMID: 30919934; c.550del, p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30919934) and in unknown phase with a likely pathogenic variant in one patient (c.2440-1G>A, 0.25 pts, PMID: 30564623, LOVD Individual #00222689) (PM3_Very Strong). At least one individual with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 17994539; PP4_Moderate). The Grpmax population frequency of this variant is 0.0003738 in gnomAD v4.1.0 (28/74900 African/African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting not met). The computational predictor REVEL gives a score of 0.881, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). A mini-gene assay showed that this variant may result in exon 11 skipping in a very small minority of transcripts; however, significant expression of transcripts with the normal annotated splice pattern was maintained (PMID: 32668095; PVS1_RNA not met). 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; 04/01/2026): PM3_Very Strong, PP4_Moderate, PP3.

Met criteria codes

PM3_Very Strong	✔	This variant has been identified in at least 8 individuals with features consistent with LGMD (PMID: 30989743, 10484770, 30564623, 17994539; LOVD CAPN3_000018; ClinVar SCV000645479.8 internal data communication), including confirmed in trans with a likely pathogenic or pathogenic variant in one case with LGMD (c.1711del p.(Leu571SerfsTer23), 1.0 pt, PMID: 17994539, 26404900), one case with hyperCKemia (c.1469G>A p.(Arg490Gln), 1.0 pt, PMID: 18854869, 14578192), and one case with chronic proximal muscle weakness (c.1715G>A (p.Arg572Gln), 1.0 pt, ClinVar SCV000645479.8 internal data communication). It has also been reported in unknown phase with a pathogenic variant in at least two patients (c.2182C>T p.(Gln728Ter), 0.5 pts, PMID: 30919934; c.550del, p.(Thr184ArgfsTer36), 0.5 pts, PMID: 30919934) and in unknown phase with a likely pathogenic variant in one patient (c.2440-1G>A, 0.25 pts, PMID: 30564623, LOVD Individual #00222689) (PM3_Very Strong). Currently 4.25 pts c.1711del p.(Leu571SerfsTer23) can be independently classified as at least LP: PM2_Supporting, PVS1 Co-occurrence: c.1466G>A is in gnomAD 2.1.0 c.550del p.(Thr184ArgfsTer36): different haplotypes c.2182C>T p.(Gln728Ter): not in gnomAD v2, co-occurrence cannot be assessed. Independently P (PM2_Supporting, PVS1, PP1, PP4) c.1469G>A p.(Arg490Gln): different haplotypes c.319G>T (p.Glu107Ter) is not in gnomAD v2, co-occurrence cannot be assessed c.1715G>A (p.Arg572Gln): different haplotypes. Independently at least LP (PP1, PP4, PP3, PM2_Supporting, PM3) Note, Magri 2015, Milic 2008 and Richard 1999, all report the same Italian patient. Unscored: ClinVar submissions LOVD Individual #00220999 (Nallamilli 2018) heterozygous for for c.1466G>A (p.Arg489Gln) c.2051-3C>G (provisionally curated, looks like will stay at VUS) LOVD Individual #00214077 (Richard 1999) heterozygous for c.1466G>A (p.Arg489Gln) and c.946-1G>A (not curated, Splice AI 0.92) duplicate with Saenz (2005) Unscoreable cases: LOVD Individual #00221940 (Nallamilli 2018) homozygous for c.1466G>A (p.Arg489Gln) and c.319G>T (p.Glu107Ter), indicating they are in cis. Cannot check co-occurrence prediction because p.(Glu107Ter) not in v2 exomes. not scored. LOVD Individual #00221248 (Nallamilli 2018) heterozygous for

c.1466G>A (p.Arg489Gln) and c.319G>T (p.Glu107Ter), phase not determined. Do not score - same variants shown to be in cis in another individual.

PP4_Moderate	✔	At least one individual with this variant and a second presumed diagnostic CAPN3 variant displayed progressive limb girdle muscle weakness and significantly reduced calpain-3 protein expression in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 17994539; PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.881, which is above the LGMD VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: no splice effect. GENEie: no cryptic site, benign, ML score 0.0.

Not Met criteria codes

PM5	✖	c.1465C>T p.(Arg489Trp): P in ClinVar, on priority list to be curated
PM2	✖	The Grpmax population frequency of this variant is 0.0003738 in gnomAD v4.1.0 (28/74900 African/African American chromosomes), which is greater than the ClinGen LGMD VCEP threshold (≤0.0001). Therefore, PM2_Supporting is not met.
PVS1	✖	The NM_000070.3: c.1466G>A variant in CAPN3 is a missense variant expected to result in the substitution of arginine for glutamine at residue 489, p.(Arg489Gln). A mini-gene assay showed that this variant may result in exon 11 skipping in a very small minority of transcripts; however, significant expression of transcripts with the normal annotated splice pattern was maintained (PMID: 32668095; PVS1_RNA not met).

Curation History

Showing 1 to 1 of 1 rows

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