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# *Variant: NM_000070.3(CAPN3):c.1333G>A (p.Gly445Arg)*

Version: 1.0

*CA7511320*

*284515 (ClinVar)*

**Gene**: CAPN3 (HGNC:825)
**Condition**: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 538c31ee-3874-421e-b6b8-34691d673b10
**Approved on**: 2026/5/1
**Published on**: 2026/5/7

## *HGVS expressions*

**NM_000070.3(CAPN3):c.1333G>A (p.Gly445Arg)**
**NM_000070.3:c.1333G>A**
NC_000015.10:g.42399631G>A
CM000677.2:g.42399631G>A
NC_000015.9:g.42691829G>A
CM000677.1:g.42691829G>A
NC_000015.8:g.40479121G>A
NG_008660.1:g.56529G>A
ENST00000349748.8:c.1189G>A
ENST00000357568.8:c.1333G>A
ENST00000397163.8:c.1333G>A
ENST00000466369.5:n.1842G>A
ENST00000483208.5:n.1564G>A
ENST00000495723.1:n.1564G>A
ENST00000549793.5:n.1564G>A
ENST00000638141.2:n.1204G>A
ENST00000673658.1:n.317G>A
ENST00000673705.1:c.288G>A
ENST00000318023.11:c.1189G>A
ENST00000349748.7:c.1189G>A
ENST00000357568.7:c.1333G>A
ENST00000397163.7:c.1333G>A
NM_000070.2:c.1333G>A
NM_024344.1:c.1333G>A
NM_173087.1:c.1189G>A
NM_024344.2:c.1333G>A
NM_173087.2:c.1189G>A

**Pathogenic**

**Met criteria codes** 6

PP3 | PP4_Moderate | PM3_Strong | PM2_Supporting | PP1_Moderate | PS2_Supporting

## 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.1333G>A variant in CAPN3 is a missense variant predicted to cause substitution of glycine by arginine at amino acid 445 (p.Gly445Arg). This variant has been detected in 6 unrelated patients with LGMD (PMID: 28403181, 38494715, 30919934, 26301378, 34720847), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 30919934), confirmed in trans with a likely pathogenic or pathogenic variant in two patients (c.1746-20G>C, 1.0 pts, PMID: 34720847; c.1505T>C p.(Ile502Thr), 1.0 pt, PMID: 34720847), and in unconfirmed phase with a pathogenic variant in another patient (c.1746-20G>C, 0.5 pts, PMID: 26301378) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness and low calpain-3 protein expression, which is specific for CAPN3-related LGMD (PP4_Moderate; PMID: 34720847). This variant has also been reported to co-segregate with autosomal recessive LGMD in two affected family members from one family (PMID: 30919934; PP1_Moderate). In one individual with LGMD, this variant was identified as a de novo occurrence with confirmed parental relationships (PS2_Supporting; PMID: 38494715). The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.0000089 in gnomAD v4.1.1 (5/1175210 European (non-Finnish) chromosomes), which is lower than the ClinGen LGMD VCEP threshold (0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.993, 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 (specifications v2.0.0; 05/01/2026): PM3_Strong, PP4_Moderate, PP1_Moderate, PS2_Supporting, PM2_Supporting, PP3.**

**Met criteria codes**

| | |
|---|---|
| **PP3** ✔ | The computational predictor REVEL gives a score of 0.993, which is above the LGMD VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3). SpliceAI: 0.00 |
| **PP4_Moderate** ✔ | 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 (PP4_Moderate; PMID: 34720847). |
| **PM3_Strong** ✔ | The variant has been detected in 6 unrelated patients with LGMD (PMID: 28403181, 38494715, 30919934, 26301378, 34720847), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 30919934), confirmed in trans with a likely pathogenic or pathogenic variant in two patients (c.1746-20G>C, 1.0 pts, PMID: 34720847; c.1505T>C p.(Ile502Thr), 1.0 pt, PMID: 34720847), and in unconfirmed phase with a pathogenic variant in another patient (c.1746-20G>C, 0.5 pts, PMID: 26301378) (PM3_Strong). |
| **PM2_Supporting** ✔ | The upper bound of the 95% confidence interval of the Grpmax variant allele frequency is 0.0000089 in gnomAD v4.1.1 (5/1175210 European (non-Finnish) chromosomes), which is lower than the ClinGen LGMD VCEP threshold (0.0001) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting). |
| **PP1_Moderate** ✔ | This variant has also been reported to co-segregate with autosomal recessive LGMD in two affected family members from one family (PMID: 30919934; PP1_Moderate). |
| **PS2_Supporting** ✔ | This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual with LGMD (PS2_Supporting; PMID: 38494715). |

## Curation History

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