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.701G>A (p.Gly234Glu)

Version: 1.0

CA16609628

501754 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6a245e3c-eec4-47f4-9fd5-85b38f7df103
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3:c.701G>A
NM_000070.3(CAPN3):c.701G>A (p.Gly234Glu)
NC_000015.10:g.42388996G>A
CM000677.2:g.42388996G>A
NC_000015.9:g.42681194G>A
CM000677.1:g.42681194G>A
NC_000015.8:g.40468486G>A
NG_008660.1:g.45894G>A
ENST00000349748.8:c.701G>A
ENST00000357568.8:c.701G>A
ENST00000397163.8:c.701G>A
ENST00000466369.5:n.1210G>A
ENST00000483208.5:n.932G>A
ENST00000495723.1:n.932G>A
ENST00000549793.5:n.932G>A
ENST00000638141.2:n.716G>A
ENST00000673705.1:c.70+4444G>A
ENST00000318023.11:c.701G>A
ENST00000349748.7:c.701G>A
ENST00000357568.7:c.701G>A
ENST00000397163.7:c.701G>A
NM_000070.2:c.701G>A
NM_024344.1:c.701G>A
NM_173087.1:c.701G>A
NM_024344.2:c.701G>A
NM_173087.2:c.701G>A

Pathogenic

Met criteria codes 4

PP3 PM3_Strong PP4_Strong PM2_Supporting

Not Met criteria codes 1

PS3

Evidence Links 1

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*

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.701G>A variant in CAPN3 is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid 234 (p.Gly234Glu). This variant has been detected in at least 8 individuals with limb girdle muscular dystrophy, including in a homozygous state in two patients (1.0 pt, PMID: 27500519, 17994539) and in trans with a likely pathogenic or pathogenic variant in at least one patient (c.1319G>A p.(Arg440Gln), 1.0 pt, PMID: 17994539) (PM3_Strong). At least one patient with this variant displayed a clinical suspicion of limb girdle muscular dystrophy and absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 17994539). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.86, which exceeds the 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; 01/09/2025): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.86, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3).
PM3_Strong	✔	This variant has been detected in at least 8 individuals with limb girdle muscular dystrophy, including in a homozygous state in two patients (1.0 pt, PMID: 27500519, 17994539) and in trans with a pathogenic variant in at least one patient (c.1319G>A p.(Arg440Glu), 1.0 pt, PMID: 17994539) (PM3_Strong).
PP4_Strong	✔	At least one patient with this variant displayed a clinical suspicion of limb girdle muscular dystrophy and absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 17994539).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).

Not Met criteria codes

PS3	✖	Functional assays have suggested this variant reduces calpain-3 autocatalytic activity (PMID: 9642272), but the LGMD VCEP has determined that this type of assay has not yet been sufficiently validated. Functional assay demonstrating that variants cause changes in autolytic activity and/or connectin/titin binding activity. Not scoreable under PS3 according to current VCEP specifications. PubMed:9642272

Curation History

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