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Variant: NM_000070.3(CAPN3):c.700G>A (p.Gly234Arg)

Version: 1.0

CA10604244

282623 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa328ce8-3476-431d-87d9-30045b2b1733
Approved on: 2025/1/7
Published on: 2025/1/7

HGVS expressions

NM_000070.3(CAPN3):c.700G>A (p.Gly234Arg)
NM_000070.3:c.700G>A
NC_000015.10:g.42388995G>A
CM000677.2:g.42388995G>A
NC_000015.9:g.42681193G>A
CM000677.1:g.42681193G>A
NC_000015.8:g.40468485G>A
NG_008660.1:g.45893G>A
ENST00000349748.8:c.700G>A
ENST00000357568.8:c.700G>A
ENST00000397163.8:c.700G>A
ENST00000466369.5:n.1209G>A
ENST00000483208.5:n.931G>A
ENST00000495723.1:n.931G>A
ENST00000549793.5:n.931G>A
ENST00000638141.2:n.715G>A
ENST00000673705.1:c.70+4443G>A
ENST00000318023.11:c.700G>A
ENST00000349748.7:c.700G>A
ENST00000357568.7:c.700G>A
ENST00000397163.7:c.700G>A
NM_000070.2:c.700G>A
NM_024344.1:c.700G>A
NM_173087.1:c.700G>A
NM_024344.2:c.700G>A
NM_173087.2:c.700G>A

Pathogenic

Met criteria codes 6

PP1 PP3 PM3 PM5 PP4_Strong PM2_Supporting

Not Met criteria codes 19

PP2 BA1 PM4 PM6 BS2 BS1 BS4 BS3 PS1 PS2 PS3

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*

PS4 BP4 BP3 BP1 BP2
PVS1 BP5 BP7

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.700G>A variant in CAPN3 is a missense variant predicted to cause substitution of glycine by arginine at amino acid 234 (p.Gly234Arg). This variant has been detected in at least four unrelated individuals with LGMD (PMID: 26484845, 32896923, 34720847, 37589857), including confirmed in trans and in unknown phase with a pathogenic variant (c.1746-20C>G, 1.5 pts, PMID: 34720847, 37589857) (PM3). At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 34720847). The variant was also reported to co-segregate with the disease in two affected family members from a single family (PP1; PMID: 37589857). This variant is absent from gnomAD v2.1.1 and v.3.1.2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.93, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3). Another missense variant at the same codon, c.701G>A p.(Gly234Glu), has been classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5). 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; 01/07/2025): PM3, PP4_Strong, PP1, PM2_Supporting, PP3, PM5.

Met criteria codes

PP1	✔	The variant was also reported to co-segregate with the disease in two affected family members from a single family (PP1; PMID: 37589857). (capped with PP4_Strong)
PP3	✔	The computational predictor REVEL gives a score of 0.93, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3).
PM3	✔	This variant has been detected in at least four unrelated individuals with LGMD (PMID: 26484845, 32896923, 34720847, 37589857), including confirmed in trans and in unknown phase with a pathogenic variant (c.1746-20C>G, 1.5 pts, PMID: 34720847, 37589857) (PM3).
PM5	✔	Another missense variant at the same codon, c.701G>A p.(Gly234Glu), has been classified as pathogenic for autosomal recessive limb girdle muscular dystrophy by the LGMD VCEP (PM5).
PP4_Strong	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 34720847).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v.3.1.2 (PM2_Supporting).

Not Met criteria codes

PP2	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BA1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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