

Variant: *NM_000070.3(CAPN3):c.633G>C (p.Lys211Asn)*

Version: 1.0

CA10604967 [↗](#)

284946 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))

Condition: autosomal recessive limb-girdle muscular dystrophy
([MONDO:0015152](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: d6ad0238-1324-4d4a-8b8e-1820bc8b1a69

Approved on: 2025/1/7

Published on: 2025/1/7

HGVS expressions

NM_000070.3:c.633G>C

NM_000070.3(CAPN3):c.633G>C (p.Lys211Asn)

NC_000015.10:g.42388928G>C

CM000677.2:g.42388928G>C

NC_000015.9:g.42681126G>C

CM000677.1:g.42681126G>C

NC_000015.8:g.40468418G>C

NG_008660.1:g.45826G>C

ENST00000349748.8:c.633G>C

ENST00000357568.8:c.633G>C

ENST00000397163.8:c.633G>C

ENST00000466369.5:n.1142G>C

ENST00000483208.5:n.864G>C

ENST00000495723.1:n.864G>C

ENST00000549793.5:n.864G>C

ENST00000638141.2:n.648G>C

ENST00000673705.1:c.70+4376G>C

ENST00000318023.11:c.633G>C

ENST00000349748.7:c.633G>C

ENST00000357568.7:c.633G>C

ENST00000397163.7:c.633G>C

NM_000070.2:c.633G>C

NM_024344.1:c.633G>C

NM_173087.1:c.633G>C

NM_024344.2:c.633G>C

NM_173087.2:c.633G>C

Likely Pathogenic

Met criteria codes 4

PP4_Strong

PM3_Supporting

PP3

PM2_Supporting

Not Met criteria codes 22

PVS1

PM6

PM1

PM5

PM4

BA1

BS1

BS4

BS3

BS2

BP5

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

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.633G>C variant in CAPN3 is a missense variant predicted to cause substitution of lysine by asparagine at amino acid 211 (p.Lys211Asn). This variant has been detected in at least nine individuals with limb girdle muscular dystrophy (PMID: 16411092, 20694146, 18055493, 18334579, 16141003, 30564623; LOVD CAPN3_000437; Washington University internal clinic data communication), including two observations in unknown phase with a variant classified as at least likely pathogenic (c.1319G>A p.(Arg440Gln), 0.5 pts, PMID: 18334579, 18055493, 20694146). At least one patient with this variant displayed progressive limb girdle muscle weakness and absent calpain-3 protein expression, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 18055493, 20694146). This variant is absent from gnomAD v2.1.1 and v3.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.859, which is above 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 Likely 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_Supporting, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong	<div><div>i</div></div>	<div>✓</div>	At least one patient with this variant displayed progressive limb girdle muscle weakness and absent calpain-3 protein expression, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 18055493, 20694146).
PM3_Supporting	<div><div>i</div></div>	<div>✓</div>	This variant has been detected in at least nine individuals with limb girdle muscular dystrophy (PMID: 16411092, 20694146, 18055493, 18334579, 16141003, 30564623; LOVD CAPN3_000437; Washington University internal data), including two observations in unknown phase with a variant classified as at least likely pathogenic (c.1319G>A p.(Arg440Gln), 0.5 pts, PMID: 18334579, 18055493, 20694146).
PP3	<div><div>i</div></div>	<div>✓</div>	The computational predictor REVEL gives a score of 0.859, which is above the VCEP threshold of 0.70, evidence that correlates with impact to CAPN3 function (PP3).
PM2_Supporting	<div><div>i</div></div>	<div>✓</div>	This variant is absent from gnomAD v2.1.1 and v3.1.1 (PM2_Supporting).

Not Met criteria codes

PVS1	<div><div>i</div></div>	<div>✗</div>	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6		<div>✗</div>	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		<div>✗</div>	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline			
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4		✖	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
BS2		✖	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
BP4		✖	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
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

