

Variant: *NM_000070.3(CAPN3):c.1524G>A (p.Glu508=)*

Version: 1.0

CA10605515 [↗](#)

286592 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 4e074784-84ce-4699-95c1-9966ae667481

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HGVS expressions

NM_000070.3:c.1524G>A

NM_000070.3(CAPN3):c.1524G>A (p.Glu508=)

NC_000015.10:g.42401810G>A

CM000677.2:g.42401810G>A

NC_000015.9:g.42694008G>A

CM000677.1:g.42694008G>A

NC_000015.8:g.40481300G>A

NG_008660.1:g.58708G>A

ENST00000349748.8:c.1380G>A

ENST00000357568.8:c.1524G>A

ENST00000397163.8:c.1524G>A

ENST00000466369.5:n.2033G>A

ENST00000483208.5:n.1755G>A

ENST00000495723.1:n.1755G>A

ENST00000549793.5:n.1755G>A

ENST00000638141.2:n.1395G>A

ENST00000673705.1:c.309+2158G>A

ENST00000318023.11:c.1380G>A

ENST00000349748.7:c.1380G>A

ENST00000357568.7:c.1524G>A

ENST00000397163.7:c.1524G>A

NM_000070.2:c.1524G>A

NM_024344.1:c.1524G>A

NM_173087.1:c.1380G>A

NM_024344.2:c.1524G>A

NM_173087.2:c.1380G>A

Pathogenic

Met criteria codes **4**

PP4_Strong

PP3

PM2_Supporting

PM3_Strong

Not Met criteria codes **22**

PS1

PS2

PS3

PS4

BA1

PP1

PP2

PM1

PM5

PM4

PM6

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.1524G>A variant in CAPN3 is a synonymous (silent) variant (p.Glu508=) that affects the last nucleotide of exon 11. This variant has been detected in at least seven individuals with LGMD (PMID: 26404900, 17236769, 17994539, 16141003, 32528171; ClinVar SCV001423802.2 internal data communication). Of those individuals, at least three were compound heterozygous, and in at least two, the variant was confirmed in trans with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 2.0 pts, PMID: 17236769, 17994539). In addition, at least one individual was homozygous for the variant (0.5 pts, PMID: 17994539) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3 protein, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 17236769). This variant is absent from gnomAD v2.1.1 and v.3.1.2 (PM2_Supporting). The SpliceAI prediction score for this variant is 0.66 (donor loss), which is greater than the VCEP threshold of ≥ 0.50 and suggestive of an impact on splicing (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; 01/07/2025): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP4_Strong	i	✓	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: 17236769).
PP3	i	✓	The SpliceAI prediction score for this variant is 0.66 (donor loss), which is greater than the VCEP threshold of ≥ 0.50 (PP3). SG: donor site loss predicted with delta SpliceAI score of 0.66, above the threshold score ≥ 0.50 .
PM2_Supporting	i	✓	This variant is absent from gnomAD v2.1.1 and v.3.1.2 (PM2_Supporting).
PM3_Strong	i	✓	This variant has been detected in at least seven individuals with LGMD (PMID: 26404900, 17236769, 17994539, 16141003, 32528171; SCV001423802.2). Of those individuals, at least three were compound heterozygous, and in at least two, the variant was confirmed in trans with a pathogenic variant (c.550del p.(Thr184ArgfsTer36), 2.0 pts, PMID: 17236769, 17994539). In addition, at least one individual was homozygous for the variant (0.5 pts, PMID: 17994539) (PM3_Strong).

Not Met criteria codes

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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			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
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			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
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			The c.1524G>A (p.Glu508=) variant is a synonymous (silent) variant. BP7 was not applied because SpliceAI predicts an impact on splicing (donor loss score: 0.66), and the nucleotide is conserved, as shown by PhyloP (score of 9.6).
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

Curation History 		
    		
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