

Variant: NM_000070.3(CAPN3):c.1782G>A (p.Val594=)

Version: 1.0

CA489885243 [↗](#)

2738034 (ClinVar) [↗](#)

Gene: CAPN3 ([HGNC:825](#))
Condition: autosomal recessive limb-girdle muscular dystrophy ([MONDO:0015152](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: ff9e7a2b-a9b2-4b24-9710-692ab7a1823e
Approved on: 2026/4/1
Published on: 2026/5/7

HGVS expressions

NM_000070.3:c.1782G>A
NM_000070.3(CAPN3):c.1782G>A (p.Val594=)
NC_000015.10:g.42403777G>A
CM000677.2:g.42403777G>A
NC_000015.9:g.42695975G>A
CM000677.1:g.42695975G>A
NC_000015.8:g.40483267G>A
NG_008660.1:g.60675G>A
ENST00000349748.8:c.1638G>A
ENST00000357568.8:c.1782G>A
ENST00000397163.8:c.1782G>A
ENST00000466369.5:n.2291G>A
ENST00000483208.5:n.2671G>A
ENST00000495723.1:n.2671G>A
ENST00000549793.5:n.2013G>A
ENST00000638141.2:n.1653G>A
ENST00000673646.1:c.246G>A
ENST00000673705.1:c.309+4125G>A
ENST00000673813.1:n.617G>A
ENST00000318023.11:c.1638G>A
ENST00000349748.7:c.1638G>A
ENST00000357568.7:c.1782G>A
ENST00000397163.7:c.1782G>A
ENST00000397200.8:c.246G>A
ENST00000567071.5:c.241G>A
ENST00000569827.5:c.246G>A
NM_000070.2:c.1782G>A
NM_024344.1:c.1782G>A
NM_173087.1:c.1638G>A
NM_173088.1:c.246G>A
NM_024344.2:c.1782G>A
NM_173087.2:c.1638G>A
NM_173088.2:c.246G>A

Likely Pathogenic

PVS1_Strong PM3_Supporting PP4 PM2_Supporting

Not Met criteria codes 3

PS1 BP7 PP3

Evidence Links 0

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.1782G>A variant in CAPN3 is a synonymous variant that is not expected to influence the protein amino acid sequence, p.(Val594=) but affects the last nucleotide of exon 14. SpliceAI gives a delta score of 0.68 for loss of the canonical splice donor site for exon 14 and 0.63 for loss of the canonical acceptor, suggesting it may affect splicing. RNAseq analysis on RNA from blood from a carrier of this variant has demonstrated that it causes near-complete missplicing, including skipping of exons 14 and 15 as well as of exons 14-16. Both of these exon skipping events are expected to introduce a frameshift and premature truncation with nonsense mediated decay expected (ClinVar SCV006324308.1 internal data communication; PVS1_RNA_Strong). In skeletal muscle, it may be associated with skipping of exon 14 only, which would also be expected to introduce a frameshift, premature truncation, and nonsense-mediated decay. This variant has been observed in a heterozygous state in at least two individuals with progressive limb girdle muscle weakness, including in unconfirmed phase with a pathogenic variant (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, GRASP-LGMD Consortium internal data communication) and confirmed in trans with a VUS (0.25 pts, ClinVar SCV006324308.1 internal data communication) (PM3_Supporting, PP4). The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1179864 European (non-Finnish) alleles), which is less than the VCEP threshold (0.0001), meeting the criterion for PM2_Supporting. 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 2.0.0; 04/01/2026): PVS1_Strong_RNA, PM3_Supporting, PP4, PM2_Supporting.

Met criteria codes

PVS1_Strong



The NM_000070.3: c.1782G>A variant in CAPN3 is a synonymous variant that is not expected to influence the protein amino acid sequence, p.(Val594=) but affects the last nucleotide of exon 14. SpliceAI gives a delta score of 0.68 for loss of the canonical splice donor site for exon 14 and 0.63 for loss of the canonical acceptor, suggesting it may affect splicing. RNAseq analysis on RNA from blood from a carrier of this variant has demonstrated that it causes near-complete missplicing, including skipping of exons 14 and 15 as well as of exons 14-16. Both of these exon skipping events are expected to introduce a frameshift and premature truncation with nonsense mediated decay expected (ClinVar SCV006324308.1 internal data communication; PVS1_RNA_Strong). In skeletal muscle, it may be associated with skipping of exon 14 only, which would also be expected to introduce a frameshift, premature truncation, and nonsense-mediated decay. SCV006324308.1: "RNA studies showed near complete mis-splicing, including exon 14-15 skipping and exon 14-15-16 skipping of the CAPN3 transcript". through a request for additional data, the RNAseq analysis report from RNA4RD was provided (from Sandra Cooper), estimating 94% loss of canonical splicing skipping of exon 14 is out of frame skipping of exons 14-15 is out of frame skipping of exons 14-16 is out of frame

PM3_Supporting



This variant has been observed in a heterozygous state in at least two individuals with progressive limb girdle muscle weakness, including in unconfirmed phase with a pathogenic variant (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 0.5 pts, GRASP-LGMD Consortium internal data communication) and confirmed in trans with a

VUS (0.25 pts, ClinVar SCV006324308.1 internal data communication) (PM3_Supporting this variant is not in gnomAD v2 and so co-occurrence cannot be assessed

PP4			This variant has been observed with a second presumed diagnostic CAPN3 variant in at least one individual who displayed progressive limb girdle muscle weakness (GRASP-LGMD Consortium internal data communication; ClinVar SCV006324308.1) (PP4).
PM2_Supporting			The Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000001695 (2/1179864 European (non-Finnish) alleles, which is less than the VCEP threshold (0.0001), meeting the criterion for PM2_Supporting.

Not Met criteria codes

PS1			curated variant: delta 0.63 for acceptor loss (ref 0.97, alt 0.34) delta 0.68 for donor loss (ref 0.88, alt 0.19) NIF impact: -87%, -82%, -38% comparison variants: c.1782+2T>C reported in PMID: 31268554 delta 0.64 for acceptor loss (ref 0.97, alt 0.32) - comparable delta 0.88 for donor loss (ref 0.88, alt 0) - slightly higher NIF impact -100%, -99%, -90% GENEie considers this variant to have a different impact c.1782+1G>A reported in PMID: 39103709, 35169782 delta 0.63 for acceptor loss (ref 0.97, alt 0.34) - same delta 0.88 for donor loss (ref 0.88, alt 0) - slightly higher c.1782+1G>T reported in PMID: 31268554 delta 0.7 for acceptor loss (ref 0.97, alt 0.27) - comparable delta 0.88 for donor loss (ref 0.88, alt 0) - slightly higher PS1_Moderate if a comparison variant considered to have same predicted effect with equivalent prediction strength and classified at P, PS1_Supporting if LP 1 or 2 Bayesian pts would not be sufficient to upgrade the classification (currently at 7) curation of comparison variants not pursued at this time
BP7			Synonymous variant located in a splice region and predicted/experimentally shown to affect splicing.
PP3			The NM_000070.3: c.1782G>A variant in CAPN3 is a synonymous variant that is not expected to influence the protein amino acid sequence, p.(Val594=). It affects the last nucleotide of exon 14 and is predicted to affect splicing with a SpliceAI delta score of 0.68 for loss of the canonical splice donor site for exon 14 and 0.63 for loss of the canonical acceptor. Skipping of exon 14, which is out of frame, would be expected to introduce a frameshift. Do not apply if PVS1_RNA applied at any strength. Splice AI delta 0.68 for donor loss (ref 0.88, alt 0.19) delta 0.63 for acceptor loss (ref 0.97, alt 0.34) skipping of exon 14, which is out of frame, seems like most likely outcome GENEie 75% probability splice altering NIF impact: U5 -87% U1 -82% U6 -38% exon 14 skipping observed in 62 samples in SpliceVault

Curation History



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