Variant: NM_000070.3(CAPN3):c.1115+5G>C

Version: 1.0

CA10588583

265521 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 512b7650-8fed-496d-9558-a71fb2650d98
Approved on: 2025-06-03
Published on: 2025-07-08

HGVS expressions

NM_000070.3:c.1115+5G>C
NM_000070.3(CAPN3):c.1115+5G>C
NC_000015.10:g.42394346G>C
CM000677.2:g.42394346G>C
NC_000015.9:g.42686544G>C
CM000677.1:g.42686544G>C
NC_000015.8:g.40473836G>C
NG_008660.1:g.51244G>C
ENST00000349748.8:c.971+5G>C
ENST00000357568.8:c.1115+5G>C
ENST00000397163.8:c.1115+5G>C
ENST00000466369.5:n.1624+5G>C
ENST00000483208.5:n.1346+5G>C
ENST00000495723.1:n.1346+5G>C
ENST00000549793.5:n.1346+5G>C
ENST00000638141.2:n.986+5G>C
ENST00000673658.1:n.99+5G>C
ENST00000673705.1:c.71-2454G>C
ENST00000318023.11:c.971+5G>C
ENST00000349748.7:c.971+5G>C
ENST00000357568.7:c.1115+5G>C
ENST00000397163.7:c.1115+5G>C
NM_000070.2:c.1115+5G>C
NM_024344.1:c.1115+5G>C
NM_173087.1:c.971+5G>C
NM_024344.2:c.1115+5G>C
NM_173087.2:c.971+5G>C

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PP4

Not Met criteria codes 2

PM3 PS1

Evidence Links 0

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.1115+5G>C variant in CAPN3 occurs in the splice donor region of intron 8 and is predicted to disrupt the splice donor site, with a SpliceAI score of 0.83. It is also predicted to disrupt the splice acceptor site of exon 8, with a SpliceAI score of 0.70. RNAseq analysis demonstrated this variant results in skipping of exon 8, which is expected to disrupt the reading frame and introduce a premature stop codon, leading to nonsense mediated decay in a gene in which loss of function is an established mechanism of disease (PMID: 32646536; PVS1_RNA). This variant has been reported in one individual with progressive muscle weakness, elevated CK and a myopathic muscle biopsy (PP4), where it was observed in trans with a variant of uncertain significance (PMID: 32646536; PM3_Supporting not met). This variant is absent from gnomAD v.4.1.0 (PM2_Supporting). 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; 06/03/2025): PVS1_RNA, PP4, PM2_Supporting.

Met criteria codes

PM2_Supporting	ⓘ	✓	This variant is absent from gnomAD v.4.1.0, meeting the criteria for PM2_Supporting. 15:42686544 not found in gnomAD v 4.1.0
PVS1	ⓘ	✓	The NM_000070.3: c.1115+5G>C variant in CAPN3 occurs in the splice donor region of intron 8 and is predicted to disrupt the splice donor site, with a SpliceAI score of 0.83. It is also predicted to disrupt the splice acceptor site of exon 8, with a SpliceAI score of 0.70. RNAseq analysis demonstrated this variant results in skipping of exon 8, which is expected to disrupt the reading frame and introduce a premature stop codon, leading to nonsense mediated decay in a gene in which loss of function is an established mechanism of disease (PMID: 32646536; PVS1_RNA).
PP4	ⓘ	✓	At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed progressive muscle weakness, elevated CK and a myopathic muscle biopsy consistent with LGMD (PMID: 32646536; PP4).

Not Met criteria codes

PM3	ⓘ	✗	This variant has been reported in one individual with features consistent with LGMD, where it was observed in trans with a variant of uncertain significance (PMID: 32646536; PM3_Supporting not met). c.506G>A p.(Arg169His) has not yet been curated but is VUS in ClinVar and benign frequency codes do not apply
PS1	ⓘ	✗	3 variants affecting same splice donor site (at +1/2) are LP/P in ClinVar, but these were not evaluated further because a Pathogenic classification already reached.

Curation History

Showing 1 to 1 of 1 rows