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Variant: NM_000070.3(CAPN3):c.2279dup (p.Asn760fs)

Version: 1.0

CA7511816

289082 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 16c18ae8-647c-4f34-a243-eb5313257a22
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3:c.2279dup
NM_000070.3(CAPN3):c.2279dup (p.Asn760fs)
NC_000015.10:g.42410899dup
CM000677.2:g.42410899dup
NC_000015.9:g.42703097dup
CM000677.1:g.42703097dup
NC_000015.8:g.40490389dup
NG_008660.1:g.67797dup
ENST00000337571.9:c.284dup
ENST00000349748.8:c.2003dup
ENST00000357568.8:c.2261dup
ENST00000397163.8:c.2279dup
ENST00000397204.9:c.284dup
ENST00000466222.7:n.724dup
ENST00000466369.5:n.2770dup
ENST00000495723.1:n.3150dup
ENST00000549793.5:n.2492dup
ENST00000562199.2:c.283dup
ENST00000567817.6:c.68dup
ENST00000568153.2:c.145dup
ENST00000569136.6:c.284dup
ENST00000638141.2:n.2018dup
ENST00000673646.1:c.843dup
ENST00000673684.1:n.261dup
ENST00000673692.1:c.284dup
ENST00000673705.1:c.822dup
ENST00000673743.1:c.182dup
ENST00000673750.1:c.284dup
ENST00000673771.1:c.284dup
ENST00000673774.1:n.1412dup
ENST00000673839.1:c.284dup
ENST00000673851.1:c.284dup
ENST00000673854.1:n.5701dup
ENST00000673886.1:c.284dup
ENST00000673890.1:c.284dup
ENST00000673928.1:c.284dup
ENST00000673936.1:c.284dup

ENST00000673939.1:c.*73dup
ENST00000673950.1:n.553dup
ENST00000673978.1:c.422dup
ENST00000673987.1:c.*73dup
ENST00000674011.1:c.*73dup
ENST00000674018.1:c.284dup
ENST00000674027.1:n.430dup
ENST00000674041.1:c.284dup
ENST00000674052.1:c.503dup
ENST00000674093.1:c.284dup
ENST00000674119.1:c.284dup
ENST00000674135.1:c.461dup
ENST00000674139.1:c.284dup
ENST00000674146.1:c.284dup
ENST00000674149.1:c.284dup
ENST00000318023.11:c.2135dup
ENST00000337571.8:c.284dup
ENST00000349748.7:c.2003dup
ENST00000356316.7:c.284dup
ENST00000357568.7:c.2261dup
ENST00000397163.7:c.2279dup
ENST00000397200.8:c.743dup
ENST00000397204.8:c.284dup
ENST00000466222.6:n.1202dup
ENST00000561817.5:c.284dup
ENST00000562199.1:n.283dup
ENST00000564503.5:c.322dup
ENST00000565274.5:c.457dup
ENST00000565559.5:c.461dup
ENST00000567817.5:c.95dup
ENST00000568153.1:c.16dup
ENST00000569136.5:c.284dup
ENST00000569827.5:c.611dup
NM_000070.2:c.2279dup
NM_024344.1:c.2261dup
NM_173087.1:c.2003dup
NM_173088.1:c.743dup
NM_173089.1:c.284dup
NM_173090.1:c.284dup
NM_024344.2:c.2261dup
NM_173087.2:c.2003dup
NM_173088.2:c.743dup
NM_173089.2:c.284dup
NM_173090.2:c.284dup

Pathogenic

Met criteria codes 4

PM3_Supporting PP4 PM2 PVS1

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.2279dup p.(Asn760LysfsTer5) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 22/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least four individuals with LGMD (PMID: 18055493, 30564623; LOVD CAPN3_000399), including in trans with a variant not yet curated by the VCEP and considered VUS in two cases (0.5 pts) (PM3_Supporting). At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4). The highest population minor allele frequency of this variant is 0.000008797 (1/113680 exome alleles) in the European (non-Finnish) population in gnomAD v2.1.1, which is less than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (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; 01/09/2025): PVS1, PM3_Supporting, PP4, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been detected in at least four individuals with LGMD (PMID: 18055493, 30564623; LOVD CAPN3_000399), including in trans with a variant not yet curated by the VCEP and considered VUS in two cases (0.5 pts) (PM3_Supporting).
PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4).
PM2	✔	The highest population minor allele frequency of this variant is 0.000008797 (1/113680 exome alleles) in the European (non-Finnish) population in gnomAD v2.1.1, which is less than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PVS1	✔	The NM_000070.3: c.2279dup p.(Asn760LysfsTer5) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 22/24 leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Curation History

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