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Variant: NM_000070.3(CAPN3):c.2290del (p.Asp764fs)

Version: 1.0

CA10606870

497201 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4977f95d-5881-4fad-8cc4-c3eba12331d8
Approved on: 2025/5/3
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HGVS expressions

NM_000070.3(CAPN3):c.2290del (p.Asp764fs)
NM_000070.3:c.2290del
NC_000015.10:g.42410910del
CM000677.2:g.42410910del
NC_000015.9:g.42703108del
CM000677.1:g.42703108del
NC_000015.8:g.40490400del
NG_008660.1:g.67808del
ENST00000337571.9:c.295del
ENST00000349748.8:c.2014del
ENST00000357568.8:c.2272del
ENST00000397163.8:c.2290del
ENST00000397204.9:c.295del
ENST00000466222.7:n.735del
ENST00000466369.5:n.2781del
ENST00000495723.1:n.3161del
ENST00000549793.5:n.2503del
ENST00000562199.2:c.294del
ENST00000567817.6:c.79del
ENST00000568153.2:c.156del
ENST00000569136.6:c.295del
ENST00000638141.2:n.2029del
ENST00000673646.1:c.854del
ENST00000673684.1:n.272del
ENST00000673692.1:c.295del
ENST00000673705.1:c.833del
ENST00000673743.1:c.193del
ENST00000673750.1:c.295del
ENST00000673771.1:c.295del
ENST00000673774.1:n.1423del
ENST00000673839.1:c.295del
ENST00000673851.1:c.295del
ENST00000673854.1:n.5712del
ENST00000673886.1:c.295del
ENST00000673890.1:c.295del
ENST00000673928.1:c.295del
ENST00000673936.1:c.295del

ENST00000673939.1:c.*84del
ENST00000673950.1:n.564del
ENST00000673978.1:c.433del
ENST00000673987.1:c.*84del
ENST00000674011.1:c.*84del
ENST00000674018.1:c.295del
ENST00000674027.1:n.441del
ENST00000674041.1:c.295del
ENST00000674052.1:c.514del
ENST00000674093.1:c.295del
ENST00000674119.1:c.295del
ENST00000674135.1:c.472del
ENST00000674139.1:c.295del
ENST00000674146.1:c.295del
ENST00000674149.1:c.295del
ENST00000318023.11:c.2146del
ENST00000337571.8:c.295del
ENST00000349748.7:c.2014del
ENST00000356316.7:c.295del
ENST00000357568.7:c.2272del
ENST00000397163.7:c.2290del
ENST00000397200.8:c.754del
ENST00000397204.8:c.295del
ENST00000466222.6:n.1213del
ENST00000561817.5:c.295del
ENST00000562199.1:n.294del
ENST00000564503.5:c.333del
ENST00000565274.5:c.468del
ENST00000565559.5:c.472del
ENST00000567817.5:c.106del
ENST00000568153.1:c.27del
ENST00000569136.5:c.295del
ENST00000569827.5:c.622del
NM_000070.2:c.2290del
NM_024344.1:c.2272del
NM_173087.1:c.2014del
NM_173088.1:c.754del
NM_173089.1:c.295del
NM_173090.1:c.295del
NM_024344.2:c.2272del
NM_173087.2:c.2014del
NM_173088.2:c.754del
NM_173089.2:c.295del
NM_173090.2:c.295del

Pathogenic

Met criteria codes 4

PM3_Strong PVS1 PM2_Supporting PP4

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.2290del p.(Asp764ThrfsTer12) 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 reported in at least three patients with features consistent with LGMD, including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 31671740, LOVD Individual #00416186) and confirmed in trans with a pathogenic variant in two patients (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 1.0 pt x2, LOVD Individual #00214755; ClinVar SCV002227607.3 personal data communication) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic variant in CAPN3 had a clinical diagnosis of LGMD (LOVD Individual #00214755; PP4). The highest minor allele frequency of this variant is 0.00004472 (2/44722 exome chromosomes) for the Admixed American population in gnomAD v4.1.0, which is lower 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; 05/03/2025): PVS1, PM3_Strong, PP4, PM2_Supporting.

Met criteria codes

PM3_Strong	✔	This variant has been reported in at least three patients with features consistent with LGMD, including in a homozygous state in one patient without reported familial consanguinity (0.5 pts, PMID: 31671740, LOVD Individual #00416186) and confirmed in trans with a pathogenic variant in two patients (c.2362_2363delinsTCATCT p.(Arg788SerfsTer14), 1.0 pt x2, LOVD Individual #00214755; ClinVar SCV002227607.3 personal data communication) (PM3_Strong).
PVS1	✔	The NM_000070.3: c.2290del p.(Asp764ThrfsTer12) 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).
PM2_Supporting	✔	The highest minor allele frequency of this variant is 0.00004472 (2/44722 exome chromosomes) for the Admixed American population in gnomAD v4.1.0, which is lower than the LGMD VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4	✔	At least one patient with this variant and a second presumed diagnostic variant in CAPN3 had a clinical diagnosis of LGMD (LOVD Individual #00214755; PP4).

Curation History

Showing 1 to 1 of 1 rows

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