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Variant: NM_000070.3(CAPN3):c.1322del (p.Gly441fs)

Version: 1.0

CA10603798

281062 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1f4d32ca-8def-4336-8bf4-8de623cb642f
Approved on: 2025/10/7
Published on: 2025/11/11

HGVS expressions

NM_000070.3(CAPN3):c.1322del (p.Gly441fs)
NM_000070.3:c.1322delG
NM_000070.3:c.1322del
NC_000015.10:g.42399620del
CM000677.2:g.42399620del
NC_000015.9:g.42691818del
CM000677.1:g.42691818del
NC_000015.8:g.40479110del
NG_008660.1:g.56518del
ENST00000349748.8:c.1178del
ENST00000357568.8:c.1322del
ENST00000397163.8:c.1322del
ENST00000466369.5:n.1831del
ENST00000483208.5:n.1553del
ENST00000495723.1:n.1553del
ENST00000549793.5:n.1553del
ENST00000638141.2:n.1193del
ENST00000673658.1:n.306del
ENST00000673705.1:c.277del
ENST00000318023.11:c.1178del
ENST00000349748.7:c.1178del
ENST00000357568.7:c.1322del
ENST00000397163.7:c.1322del
NM_000070.2:c.1322del
NM_024344.1:c.1322del
NM_173087.1:c.1178del
NM_024344.2:c.1322del
NM_173087.2:c.1178del

Pathogenic

Met criteria codes 4

PVS1 PM3 PP4_Strong PM2_Supporting

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 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.1322del p.(Gly441ValfsTer22) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 11/24, 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 six patients with clinical features consistent with LGMD2A (PMID: 15689361, 26501342, 25135358, 17702496, 17236769, 15733273), including in unconfirmed phase with a pathogenic variant in at least three patients (c.2362-2363delinsTCATCT, 0.5 pts, PMID: 15689361; c.550del, 0.5 pts x2, PMID: 17702496, 15733273) (PM3). At least one patient with this variant and a second presumed diagnostic CAPN3 variant had a clinical diagnosis of LGMD and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 15733273; PP4_Strong). The upper bound of the 95% confidence interval (95% CI) of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000008921 (5/1178404 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (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 2.0.0; 10/07/2025): PVS1, PM3, PP4_Strong, PM2_Supporting.

Met criteria codes

PVS1	✔	The NM_000070.3: c.1322del p.(Gly441ValfsTer22) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 11/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).
PM3	✔	This variant has been reported in at least six patients with clinical features consistent with LGMD2A (PMID: 15689361, 26501342, 25135358, 17702496, 17236769, 15733273), including in unconfirmed phase with a pathogenic variant in at least three patients (c.2362-2363delinsTCATCT, 0.5 pts, PMID: 15689361; c.550del, 0.5 pts x2, PMID: 17702496, 15733273) (PM3). Saenz: 0.5 pts, c.2362-2363delinsTCATCT unknown phase LGMD VCEP curation and scoring of cases entered by the Broad: PMID: 26501342 Chen et al. (2015) Patient with LGMD, reported compound heterozygote with genotype c.1322delG and c.1465C>T (p.Arg489Trp), which we haven't curated yet but is pathogenic in ClinVar (ClinVar Variation ID: 217150), PMID 25135358 Stehlíková et al. (2014) Patient 59: in unknown phase with c.2114A>G p.(Asp705Gly) , not yet curated PMID 17702496 Hanisch et al. (2007) 4. Patient 10 (7 y o), myalgia, hyperCKemia (5,365), mild myopathic inflammatory reaction on muscle biopsy, signs of myopathy on EMG. reduced 90 kDa band, absent 60 kDa band, normal 30 kDa band on WB. in unconfirmed phase with c.550delA (approved at P, 0.5 pts) German PMID: 17236769 Milic et al. Patient D25 with LGMD. Reported compound heterozygote with c.1099G>A (p.Gly367Ser) but methodology for phasing not confirmed, not in VCI (0.0 pts). Normal autolytic and proteolytic calapain-3 activity in vitro and normal expression on WB of muscle biopsy. PMID: 15733273 Todorova et al. (2005) Patient 3, unconfirmed phase with c.550delA (Pathogenic, ClinVar Variation ID: 17621) (0.5 pts). absent calpain-3 on WB. Onset at age 3 with difficulty with stairs. calf hypertrophy and scapula alata. No hip adductor, hip abductor, abdominal muscle weakness at age 11.
PP4_Strong	✔	This variant has been identified with a second presumed diagnostic CAPN3 variant in at least one individual with a clinical diagnosis of LGMD and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 15733273; PP4_Strong). PMID: 15733273 Todorova et al. (2005) Patient 3, unconfirmed phase with c.550delA (Pathogenic, ClinVar Variation ID: 17621) (0.5 pts). absent calpain-3 on WB. Onset at age 3

with difficulty with stairs. calf hypertrophy and scapula alata. No hip adductor, hip abductor, abdominal muscle weakness reported at age 11 but phenotype considered clinically consistent with a diagnosis of LGMD.

PM2_Supporting ✔

The upper bound of the 95% confidence interval (95% CI) of the Grpmax variant allele frequency in gnomAD v4.1.0 is 0.000008921 (5/1178404 European (non-Finnish) chromosomes), which is less than the ClinGen LGMD VCEP threshold (≤0.0001) (PM2_Supporting).

Curation History

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