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Variant: NM_000070.3(CAPN3):c.2148G>T (p.Glu716Asp)

Version: 1.0

CA10605085

285340 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5312322a-f38f-49be-8533-973e46b9d9c5
Approved on: 2025/6/25
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HGVS expressions

NM_000070.3(CAPN3):c.2148G>T (p.Glu716Asp)
NM_000070.3:c.2148G>T
NC_000015.10:g.42410460G>T
CM000677.2:g.42410460G>T
NC_000015.9:g.42702658G>T
CM000677.1:g.42702658G>T
NC_000015.8:g.40489950G>T
NG_008660.1:g.67358G>T
ENST00000337571.9:c.153G>T
ENST00000349748.8:c.1872G>T
ENST00000357568.8:c.2130G>T
ENST00000397163.8:c.2148G>T
ENST00000397204.9:c.153G>T
ENST00000466222.7:n.413G>T
ENST00000466369.5:n.2639G>T
ENST00000495723.1:n.3019G>T
ENST00000549793.5:n.2361G>T
ENST00000562199.2:c.152G>T
ENST00000568153.2:c.14G>T
ENST00000569136.6:c.153G>T
ENST00000638141.2:n.1887G>T
ENST00000673646.1:c.712G>T
ENST00000673684.1:n.130G>T
ENST00000673687.1:n.657G>T
ENST00000673692.1:c.153G>T
ENST00000673705.1:c.511-128G>T
ENST00000673743.1:c.51G>T
ENST00000673750.1:c.153G>T
ENST00000673771.1:c.153G>T
ENST00000673774.1:n.1281G>T
ENST00000673839.1:c.153G>T
ENST00000673851.1:c.153G>T
ENST00000673854.1:n.5570G>T
ENST00000673886.1:c.153G>T
ENST00000673890.1:c.153G>T
ENST00000673893.1:c.351G>T
ENST00000673928.1:c.153G>T

ENST00000673936.1:c.153G>T
ENST00000673939.1:c.153G>T
ENST00000673950.1:n.422G>T
ENST00000673978.1:c.291G>T
ENST00000673987.1:c.153G>T
ENST00000674011.1:c.153G>T
ENST00000674018.1:c.153G>T
ENST00000674027.1:n.208G>T
ENST00000674041.1:c.153G>T
ENST00000674052.1:c.372G>T
ENST00000674093.1:c.153G>T
ENST00000674119.1:c.153G>T
ENST00000674135.1:c.330G>T
ENST00000674139.1:c.153G>T
ENST00000674146.1:c.153G>T
ENST00000674149.1:c.153G>T
ENST00000318023.11:c.2004G>T
ENST00000337571.8:c.153G>T
ENST00000349748.7:c.1872G>T
ENST00000356316.7:c.153G>T
ENST00000357568.7:c.2130G>T
ENST00000397163.7:c.2148G>T
ENST00000397200.8:c.612G>T
ENST00000397204.8:c.153G>T
ENST00000466222.6:n.1071G>T
ENST00000561817.5:c.153G>T
ENST00000562199.1:n.152G>T
ENST00000564503.5:c.245G>T
ENST00000565274.5:c.380G>T
ENST00000565559.5:c.330G>T
ENST00000569136.5:c.153G>T
ENST00000569827.5:c.480G>T
NM_000070.2:c.2148G>T
NM_024344.1:c.2130G>T
NM_173087.1:c.1872G>T
NM_173088.1:c.612G>T
NM_173089.1:c.153G>T
NM_173090.1:c.153G>T
NM_024344.2:c.2130G>T
NM_173087.2:c.1872G>T
NM_173088.2:c.612G>T
NM_173089.2:c.153G>T
NM_173090.2:c.153G>T

Pathogenic

Met criteria codes 4

PP3 PP4_Strong PM3_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 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.2148G>T variant in CAPN3 is a missense variant predicted to cause the substitution of glutamic acid to aspartic acid at codon 716, p.(Glu716Asp). This variant has been reported in at least five individuals with features consistent with LGMD (PMID: 15689361, 32994280, 37526466; LOVD CAPN3_000296), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts; PMID: 15689361, LOVD Individual #00311346), confirmed in trans with a likely pathogenic or pathogenic variant (c.1401_1403del p.(Glu467del), 1.0 pt, PMID: 37526466), and in unknown phase with a pathogenic variant (c.967G>T p.(Glu323Ter), 0.5 pts, PMID: 15689361) (PM3_Strong). At least one patient with this variant and a second presumed diagnostic variant in CAPN3 had both a clinical diagnosis of LGMD and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 15689361; PP4_Strong). The filtering allele frequency for this variant is 0.000008232 (the upper threshold of the 95% CI of 4/11112002 European (non-Finnish) exome chromosomes in gnomAD v4.1.0), which is less than the LGMD VCEP threshold (0.0001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.84, evidence which correlates with impact to CAPN3 function (PP3). 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; 06/25/2025): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.84 (PP3).
PP4_Strong	✔	At least one patient with this variant and a second presumed diagnostic variant in CAPN3 had both a clinical diagnosis of LGMD and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PMID: 15689361; PP4_Strong). p94, calpain 60, and calpain 30 were all found to be absent in patient LOVD Individual 00214300 (Saenz et al. PMID 15689361). Calpain-3 was detected with a western conducted with protein extracted from patient muscle biopsy. Patients in this study were included based on diagnostic criteria established at the European Neuromuscular Centre Workshop (Beckmann and Bushby, 1996). Patients had to fulfill all main criteria.
PM3_Strong	✔	This variant has been reported in at least five individuals with features consistent with LGMD (PMID: 15689361, 32994280, 37526466; LOVD CAPN3_000296), including in a homozygous state in one patient without reported familial consanguinity (0.5 pts; PMID: 15689361, LOVD Individual #00311346), confirmed in trans with a likely pathogenic or pathogenic variant (c.1401_1403del p.(Glu467del), 1.0 pt, PMID: 37526466), and in unknown phase with a pathogenic variant (c.967G>T p.(Glu323Ter), 0.5 pts, PMID: 15689361) (PM3_Strong). The Saenz et al. (2005) case (PMID: 15689361) is LOVD Individual #00214300, who also has c.967G>T p.(Glu323Ter), which is approved at P independent of this case (0.5 pts; cannot check co-occurrence because 1 variant not in gnomAD v2). Patients are described as compound het in the paper and in LOVD, but method of phasing not described so conservatively consider of unknown phase. Per the supplementary table, this patient had absent calpain-3 expression on WB. Zhong et al. (2021) (PMID: 32994280) patient inclusion and exclusion criteria include the following: (1) progressive weakness involving shoulder girdle and/or pelvic girdle; (2) myopathic changes in electromyography; (3) myopathic or muscular dystrophy changes revealed by muscle biopsy; (4) DNA sequencing revealed recessive mutations in CAPN3. All recruited patients met criteria 1/2/4, with or without criteria 3. Co-segregation analysis was performed if the parents' blood samples were available. Of 124 cases, 102 "identified as compound heterozygous", 22 homozygous. Three patients with this variant submitted to LOVD: Individual #00311256 (pat25): c.2050+1G>A

supposedly in trans, not yet curated. Individual #00311339 (pat108): c.1622G>C p.(Arg541Pro) supposedly in trans, not yet curated. Individual #00311346 (pat115): homozygous, no reported consanguinity (0.5 pts). Zídková et al. (2023) (PMID: 37526466) Inclusion criteria included clinical suspicion of LGMD and variants with presumed pathogenic effect on both alleles. All patients unrelated. Confirmed in trans with c.1401_1403del p.(Glu467del) in one patient. c.1401_1403del p.(Glu467del) can be independently classified as LP. (1.0 pt) only other case in LOVD, Individual #00214043, is single heterozygous (no PMID cited).

PM2_Supporting ✔

The filtering allele frequency for this variant is 0.000008232 (the upper threshold of the 95% CI of 4/11112002 European (non-Finnish) exome chromosomes in gnomAD v4.1.0), which is less than the LGMD VCEP threshold (0.0001), meeting this criterion (PM2_Supporting).

Curation History

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