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Variant: NM_000070.3(CAPN3):c.1865_1866del (p.Glu622fs)

Version: 1.0

CA969129783

935255 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6021ade2-3dbd-4550-8c2f-4c3577844733
Approved on: 2025/8/19
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HGVS expressions

NM_000070.3(CAPN3):c.1865_1866del (p.Glu622fs)
NM_000070.3:c.1865_1866del
NC_000015.10:g.42408275_42408276del
CM000677.2:g.42408275_42408276del
NC_000015.9:g.42700473_42700474del
CM000677.1:g.42700473_42700474del
NC_000015.8:g.40487765_40487766del
NG_008660.1:g.65173_65174del
ENST00000337571.9:c.-81-1028_-81-1027del
ENST00000349748.8:c.1639-1028_1639-1027del
ENST00000357568.8:c.1847_1848del
ENST00000397163.8:c.1865_1866del
ENST00000397204.9:c.-81-1028_-81-1027del
ENST00000466369.5:n.2356_2357del
ENST00000495723.1:n.2736_2737del
ENST00000549793.5:n.2078_2079del
ENST00000565173.2:n.239_240del
ENST00000569136.6:c.-131_-130del
ENST00000638141.2:n.1654-1028_1654-1027del
ENST00000673646.1:c.429_430del
ENST00000673692.1:c.-3-1512_-3-1511del
ENST00000673705.1:c.310-1028_310-1027del
ENST00000673743.1:c.-179+135_-179+136del
ENST00000673750.1:c.-131_-130del
ENST00000673771.1:c.-131_-130del
ENST00000673839.1:c.-275_-274del
ENST00000673851.1:c.-131_-130del
ENST00000673854.1:n.4309_4310del
ENST00000673886.1:c.-131_-130del
ENST00000673890.1:c.-131_-130del
ENST00000673928.1:c.-82+135_-82+136del
ENST00000673936.1:c.-131_-130del
ENST00000673939.1:c.-81-1028_-81-1027del
ENST00000673978.1:c.-297_-296del
ENST00000673987.1:c.-131_-130del
ENST00000674011.1:c.-131_-130del
ENST00000674012.1:n.140_141del

ENST00000674018.1:c.-131_-130del
ENST00000674041.1:c.-81-1028_-81-1027del
ENST00000674052.1:c.89_90del
ENST00000674064.1:n.244_245del
ENST00000674093.1:c.-81-1028_-81-1027del
ENST00000674119.1:c.-81-1028_-81-1027del
ENST00000674135.1:c.-67_-66del
ENST00000674139.1:c.-131_-130del
ENST00000674140.1:n.1016_1017del
ENST00000674146.1:c.-131_-130del
ENST00000674149.1:c.-131_-130del
ENST00000318023.11:c.1721_1722del
ENST00000337571.8:c.-81-1028_-81-1027del
ENST00000349748.7:c.1639-1028_1639-1027del
ENST00000356316.7:c.-90-1019_-90-1018del
ENST00000357568.7:c.1847_1848del
ENST00000397163.7:c.1865_1866del
ENST00000397200.8:c.329_330del
ENST00000397204.8:c.-81-1028_-81-1027del
ENST00000561817.5:c.-81-1028_-81-1027del
ENST00000565173.1:n.194_195del
ENST00000565274.5:c.77_78del
ENST00000565559.5:c.-67_-66del
ENST00000567071.5:c.324_325del
ENST00000569136.5:c.-131_-130del
ENST00000569827.5:c.247-1028_247-1027del
NM_000070.2:c.1865_1866del
NM_024344.1:c.1847_1848del
NM_173087.1:c.1639-1028_1639-1027del
NM_173088.1:c.329_330del
NM_173089.1:c.-81-1028_-81-1027del
NM_173090.1:c.-81-1028_-81-1027del
NM_024344.2:c.1847_1848del
NM_173087.2:c.1639-1028_1639-1027del
NM_173088.2:c.329_330del
NM_173089.2:c.-81-1028_-81-1027del
NM_173090.2:c.-81-1028_-81-1027del

Pathogenic

Met criteria codes 4

PM3_Supporting PP4_Moderate PM2_Supporting 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.1865_1866del p.(Glu622GlyfsTer9) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in exon 16/24, leading to nonsense-mediated decay in a gene in which loss of function is a known disease mechanism (PVS1). This variant has been reported in at least four individuals with features consistent with LGMD (PMID: 16141003, 16650086, 10330340; LOVD CAPN3_000103), including in unconfirmed phase with a pathogenic variant in one patient (c.1250C>T p.(Thr417Met), 0.5 pts, PMID: 1665008, LOVD Individual #00214386) (PM3_Supporting). It has also been classified as Likely Pathogenic/Pathogenic by multiple submitters in ClinVar (VCV000935255.33). At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed severely reduced calpain-3 expression in skeletal muscle as well as progressive limb girdle muscle weakness, which is specific for CAPN3-related LGMD (PMID: 16650086, LOVD Individual #00214386; PP4_Moderate). The filtering allele frequency for this variant is 0.000007 in gnomAD v4.1.0 exomes (the upper bound of the 95% confidence interval of 3/1111832 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold for PM2_Supporting (0.0001), 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; 08/19/2025): PVS1, PM3_Supporting, PP4_Moderate, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been reported in at least four individuals with features consistent with LGMD (PMID: 16141003, 16650086, 10330340; LOVD CAPN3_000103), including in unconfirmed phase with a pathogenic variant in one patient (c.1250C>T p.(Thr417Met), 0.5 pts, PMID: 1665008, LOVD Individual #00214386) (PM3_Supporting). c.1865_1866del p.(Glu622GlyfsTer9) is not in gnomAD v2 and so co-occurrence cannot be evaluated. It is classified as P independently of this case.
PP4_Moderate	✔	At least one patient with this variant and a second presumed diagnostic CAPN3 variant displayed severely reduced calpain-3 expression in skeletal muscle as well as progressive limb girdle muscle weakness, which is specific for CAPN3-related LGMD (PMID: 16650086, LOVD Individual #00214386; PP4_Moderate).
PM2_Supporting	✔	The filtering allele frequency for this variant is 0.000007 in gnomAD v4.1.0 exomes (the upper bound of the 95% confidence interval of 3/1111832 European (non-Finnish) chromosomes), which is lower than the LGMD VCEP threshold for PM2_Supporting.
PVS1	✔	The NM_000070.3: c.1865_1866del p.(Glu622GlyfsTer9) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in exon 16/24, leading to nonsense-mediated decay in a gene in which loss of function is a known disease mechanism (PVS1).

Curation History

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