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Variant: NM_000070.3(CAPN3):c.1395GGA[2] (p.Glu467del)

Version: 1.0

CA7511349

553852 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: d2fdc1d2-34c4-4901-b531-6ee716a02314
Approved on: 2025/6/24
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HGVS expressions

NM_000070.3:c.1401_1403del
NM_000070.3(CAPN3):c.1395GGA[2] (p.Glu467del)
NM_000070.3:c.1395GGA[2]
NC_000015.10:g.42401687_42401689del
CM000677.2:g.42401687_42401689del
NC_000015.9:g.42693885_42693887del
CM000677.1:g.42693885_42693887del
NC_000015.8:g.40481177_40481179del
NG_008660.1:g.58585_58587del
ENST00000349748.8:c.1257_1259del
ENST00000357568.8:c.1401_1403del
ENST00000397163.8:c.1401_1403del
ENST00000466369.5:n.1910_1912del
ENST00000483208.5:n.1632_1634del
ENST00000495723.1:n.1632_1634del
ENST00000549793.5:n.1632_1634del
ENST00000638141.2:n.1272_1274del
ENST00000673705.1:c.309+2035_309+2037del
ENST00000318023.11:c.1257_1259del
ENST00000349748.7:c.1257_1259del
ENST00000357568.7:c.1401_1403del
ENST00000397163.7:c.1401_1403del
NM_000070.2:c.1401_1403del
NM_024344.1:c.1401_1403del
NM_173087.1:c.1257_1259del
NM_024344.2:c.1401_1403del
NM_173087.2:c.1257_1259del

Pathogenic

Met criteria codes 4

PM3_Very Strong | PM4 | PP4_Moderate | 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.1401_1403del variant in CAPN3 is expected to cause an in-frame deletion of one amino acid, p.(Glu467del) (PM4). This variant has been identified in at least 8 individuals with features consistent with LGMD (PMID: 16141003, 17994539, 16650086, 31555977, 18854869, 38391941, LOVD CAPN3_000200), including in a homozygous state without reported consanguinity in at least one patient (0.5 pts, PMID: 17994539, LOVD Individual # 00214553), confirmed in trans with a likely pathogenic or pathogenic variant in two patients (c.2148G>T p.(Glu716Asp), 1.0 pt, PMID: 37526466; c.967G>T (p.Glu323Ter), 1.0 pt, PMID: 38391941), and in unknown phase with a pathogenic variant in three patients (c.2242C>T p.(Arg748Ter), 0.5 pts x2 = 1.0 pt, PMID: 16141003, 18854869, LOVD Individuals 00214012, 00214187; c.1865_1866del p.(Glu622GlyfsTer9), 0.5 pts, PMID: 16650086, LOVD Individual #00214391) (PM3_Very Strong). At least one patient with this variant and a second presumed diagnostic variant in CAPN3 displayed progressive limb girdle muscle weakness and significantly reduced expression of calpain-3 protein in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 18854869; PP4_Moderate). The filtering allele frequency of this variant in gnomAD v4.1.0 exomes is 0.000027195 (the upper threshold of the 95% CI of 21/1111998 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 1.0.0; 06/24/2025): PM3_Very Strong, PP4_Moderate, PM2_Supporting, PM4.

Met criteria codes

PM3_Very Strong	✔	This variant has been identified in at least 8 individuals with features consistent with LGMD (PMID: 16141003, 17994539, 16650086, 31555977, 18854869, 38391941, LOVD CAPN3_000200), including in a homozygous state without reported consanguinity in at least one patient (0.5 pts, PMID: 17994539, LOVD Individual # 00214553), confirmed in trans with a likely pathogenic or pathogenic variant in two patients (c.2148G>T p.(Glu716Asp), 1.0 pt, PMID: 37526466; c.967G>T (p.Glu323Ter), 1.0 pt, PMID: 38391941), and in unknown phase with a pathogenic variant in three patients (c.2242C>T p.(Arg748Ter), 0.5 pts x2 = 1.0 pt, PMID: 16141003, 18854869, LOVD Individuals 00214012, 00214187; c.1865_1866del p.(Glu622GlyfsTer9), 0.5 pts, PMID: 16650086, LOVD Individual #00214391) (PM3_Very Strong). c.2148G>T p.(Glu716Asp) can be classified as LP without this case but has a final classification of P c.2242C>T p.(Arg748Ter) is independently P and is not in gnomAD v2 and so co-occurrence cannot be assessed c.1865_1866del p.(Glu622GlyfsTer9) is independently P and not in gnomAD v2 and so co-occurrence cannot be evaluated
PM4	✔	The variant is predicted to cause a change in the length of the protein due to an in-frame deletion of one amino acid (PM4). Glu467 is the second of two Glu residues. The sequence of this region includes 3 repeats of GGA, and deletion of either the first, c.1395_1397del, or the third, c.1401_1403del, result in the same protein consequence. Should this be considered a "repeat region"? Not applying this code would not change the variant classification in light of the considerable case data (PM3_Very Strong).
PP4_Moderate	✔	At least one patient with this variant and a second presumed diagnostic variant in CAPN3 displayed progressive limb girdle muscle weakness and significantly reduced expression of calpain-3 protein in skeletal muscle, which is specific for CAPN3-related LGMD (PMID: 18854869; PP4_Moderate).
PM2_Supporting	✔	The filtering allele frequency of this variant in gnomAD v4.1.0 exomes is 0.000027195 (the upper threshold of the 95% CI of 21/1111998 European (non-Finnish) chromosomes) , which is less than the ClinGen LGMD VCEP threshold

(≤0.0001) (PM2_Supporting).

Curation History

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