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Variant: NM_000070.3(CAPN3):c.756GAA[1] (p.Lys254del)

Version: 1.0

CA346886

197624 (ClinVar)

Gene: CAPN3
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 83f8a4fa-2205-4228-ab88-4021b15db376
Approved on: 2025/1/9
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HGVS expressions

NM_000070.3:c.756_758del
NM_000070.3:c.756GAA[1]
NM_000070.3(CAPN3):c.756GAA[1] (p.Lys254del)
NM_000070.3:c.759_761del
NC_000015.10:g.42389054_42389056del
CM000677.2:g.42389054_42389056del
NC_000015.9:g.42681252_42681254del
CM000677.1:g.42681252_42681254del
NC_000015.8:g.40468544_40468546del
NG_008660.1:g.45952_45954del
ENST00000349748.8:c.759_761del
ENST00000357568.8:c.759_761del
ENST00000397163.8:c.759_761del
ENST00000466369.5:n.1268_1270del
ENST00000483208.5:n.990_992del
ENST00000495723.1:n.990_992del
ENST00000549793.5:n.990_992del
ENST00000638141.2:n.774_776del
ENST00000673705.1:c.70+4502_70+4504del
ENST00000318023.11:c.759_761del
ENST00000349748.7:c.759_761del
ENST00000357568.7:c.759_761del
ENST00000397163.7:c.759_761del
NM_000070.2:c.759_761del
NM_024344.1:c.759_761del
NM_173087.1:c.759_761del
NM_024344.2:c.759_761del
NM_173087.2:c.759_761del

Pathogenic

Met criteria codes 3

PP4 PM4 PM3_Very Strong

Not Met criteria codes 1

PM2

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Evidence Links 0

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.759_761del variant in CAPN3, which is also known as c.756_758del, is predicted to cause a change in the length of the protein due to an in-frame deletion of one amino acid in a non-repeat region, p.(Lys254del) (PM4). This variant has been detected in at least 11 unrelated individuals with limb girdle muscular dystrophy (PMID: 26886200, 10330340, 16141003, 18055493, 30564623, 12461690, 35731190), including in a homozygous state in one case (0.5 pts; PMID: 18055493), confirmed in trans with a pathogenic variant in three cases (c.1468C>T p.(Arg490Trp), 1.0 pt, PMID: 12461690; c.1746-20C>G, 2.0 pts, PMID: 35731190), and in unknown phase with a pathogenic variant in one case (c.1468C>T p.(Arg490Trp), 0.5 pts, PMID: 18055493) (PM3_Very Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4). The filtering allele frequency of the variant is 0.0001933 for European (non-Finnish) genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 7/68016), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met). 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; 01/09/2025): PM4, PM3_Very Strong, PP4.

Met criteria codes

PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness or a clinical suspicion of LGMD (PP4).
PM4	✔	The NM_000070.3: c.756_758del variant in CAPN3 is predicted to cause a change in the length of the protein (p.Lys254del) due to an in-frame deletion of one amino acid in a non-repeat region (PM4).
PM3_Very Strong	✔	This variant has been detected in at least 11 unrelated individuals with LGMD (PMID: 26886200, 10330340, 16141003, 18055493, 30564623, 12461690, 35731190), including in a homozygous state in one case (0.5 pts; PMID: 18055493), confirmed in trans with a pathogenic variant in three cases (c.1468C>T p.(Arg490Trp), 1.0 pt, PMID: 12461690; c.1746-20C>G, 2.0 pts, PMID: 35731190), and in unknown phase with a pathogenic variant in one case (c.1468C>T p.(Arg490Trp), 0.5 pts, PMID: 18055493) (PM3_Very Strong).

Not Met criteria codes

PM2	✖	The filtering allele frequency of the variant is 0.0001933 for European (non-Finnish) genome alleles in gnomAD v3.1.2 (the upper threshold of the 95% CI of 7/68016), which is greater than the LGMD VCEP threshold (<0.0001) for PM2_Supporting (criterion not met).

Curation History

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