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Variant: NM_000070.3(CAPN3):c.883_886delinsCTT (p.Asp295fs)

Version: 1.0

CA347485

217160 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4f4afbc9-a388-4b58-bff6-2f853d6f023b
Approved on: 2025/6/3
Published on: 2025/7/8

HGVS expressions

NM_000070.3:c.883_886delinsCTT
NM_000070.3(CAPN3):c.883_886delinsCTT (p.Asp295fs)
NC_000015.10:g.42390034_42390037delinsCTT
CM000677.2:g.42390034_42390037delinsCTT
NC_000015.9:g.42682232_42682235delinsCTT
CM000677.1:g.42682232_42682235delinsCTT
NC_000015.8:g.40469524_40469527delinsCTT
NG_008660.1:g.46932_46935delinsCTT
ENST00000349748.8:c.801+938_801+941delinsCTT
ENST00000357568.8:c.883_886delinsCTT
ENST00000397163.8:c.883_886delinsCTT
ENST00000466369.5:n.1392_1395delinsCTT
ENST00000483208.5:n.1114_1117delinsCTT
ENST00000495723.1:n.1114_1117delinsCTT
ENST00000549793.5:n.1114_1117delinsCTT
ENST00000638141.2:n.816+938_816+941delinsCTT
ENST00000673705.1:c.70+5482_70+5485delinsCTT
ENST00000318023.11:c.801+938_801+941delinsCTT
ENST00000349748.7:c.801+938_801+941delinsCTT
ENST00000357568.7:c.883_886delinsCTT
ENST00000397163.7:c.883_886delinsCTT
NM_000070.2:c.883_886delinsCTT
NM_024344.1:c.883_886delinsCTT
NM_173087.1:c.801+938_801+941delinsCTT
NM_024344.2:c.883_886delinsCTT
NM_173087.2:c.801+938_801+941delinsCTT

Pathogenic

Met criteria codes 5

PM3_Supporting PP1_Moderate 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.883_886delinsCTT p.(Asp295LeufsTer57) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 8/24, 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 4 unrelated patients with clinical signs of LGMD (PMID: 16141003, 15733273, 17994539, 16650086, 15689361, 30919934), including in a homozygous state in one individual without reported familial consanguinity (0.5 pts, PMID: 1614100; PM3_Supporting). This variant has also been reported to co-segregate with autosomal recessive LGMD in 3 affected members of a single family (PMID: 16141003; PP1_Moderate). In addition, at least one of the patients 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 (PP4_Moderate, capped with PP1_Moderate; PMID: 16650086, 15689361). This variant is absent from gnomAD v4.1.0 (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; 06/03/2025): PVS1, PM3_Supporting, PP1_Moderate, PP4_Moderate, PM2_Supporting.

Met criteria codes

PM3_Supporting	✔	This variant has been reported in at least 4 unrelated patients with clinical signs of LGMD (PMID: 16141003, 15733273, 17994539, 16650086, 15689361, 30919934), including in a homozygous state in one individual without reported familial consanguinity (0.5 pts, PMID: 1614100; PM3_Supporting).
PP1_Moderate	✔	This variant has been reported to co-segregate with autosomal recessive LGMD in 3 affected members of a single family (PMID: 16141003; PP1_Moderate).
PP4_Moderate	✔	At least one of the patients 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 (PP4_Moderate, capped with PP1_Moderate; PMID: 15733273, 15689361).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Note that another nucleotide change (15-42390032-TG-T) predicted to result in a similar protein consequence, p.(Asp295IlefsTer57), has a FAF of 0.000028251 (22/1111988 European (non-Finnish) exome chromosomes).
PVS1	✔	The NM_000070.3: c.883_886delinsCTT p.(Asp295LeufsTer57) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 8/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1).

Curation History

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