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Variant: NM_000070.3(CAPN3):c.146G>A (p.Arg49His)

Version: 1.0

CA347493

217151 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: e6676c7c-b75a-484d-8622-2ec2a73c3b7c
Approved on: 2025/1/9
Published on: 2025/1/9

HGVS expressions

NM_000070.3(CAPN3):c.146G>A (p.Arg49His)
NM_000070.3:c.146G>A
NC_000015.10:g.42359951G>A
CM000677.2:g.42359951G>A
NC_000015.9:g.42652149G>A
CM000677.1:g.42652149G>A
NC_000015.8:g.40439441G>A
NG_008660.1:g.16849G>A
ENST00000349748.8:c.146G>A
ENST00000357568.8:c.146G>A
ENST00000397163.8:c.146G>A
ENST00000466369.5:n.540+5498G>A
ENST00000483208.5:n.540+5498G>A
ENST00000495723.1:n.540+5498G>A
ENST00000549793.5:n.540+5498G>A
ENST00000318023.11:c.146G>A
ENST00000349748.7:c.146G>A
ENST00000357568.7:c.146G>A
ENST00000397163.7:c.146G>A
NM_000070.2:c.146G>A
NM_024344.1:c.146G>A
NM_173087.1:c.146G>A
NM_024344.2:c.146G>A
NM_173087.2:c.146G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4_Strong PM3_Strong

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.146G>A variant in CAPN3 is a missense variant predicted to cause substitution of arginine by histidine at amino acid 49 (p.Arg49His). This variant has been detected in at least six unrelated individuals with limb girdle muscular dystrophy (PMID: 16650086, 17318636, 25135358; ClinVar SCV003459936.1 internal data communication, ClinVar SCV001164521.1 internal data communication), including in a homozygous state in one individual (ClinVar SCV001164521.1 internal data communication, 0.5 pts), confirmed in trans with a pathogenic variant (c.967G>T p.(Glu323Ter), 1.0 pt, PMID: 17318636), and confirmed in trans with two variants not yet curated by the VCEP and considered VUS (0.5 pts) (PM3_Strong). At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 16650086). This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting). The computational predictor REVEL gives a score of 0.84, which exceeds the VCEP threshold of ≥0.70, evidence that 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; 01/09/2025): PM3_Strong, PP4_Strong, PM2_Supporting, PP3.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.84, which exceeds the VCEP threshold of ≥0.70, evidence that correlates with impact to CAPN3 function (PP3).
PP4_Strong	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness as well as absent expression of calpain-3, which is highly specific for CAPN3-related LGMD (PP4_Strong; PMID: 16650086).
PM3_Strong	✔	This variant has been detected in at least six unrelated individuals with limb girdle muscular dystrophy (PMID: 16650086, 17318636, 25135358; SCV003459936.1, SCV001164521.1), including in a homozygous state in one individual (SCV001164521.1, 0.5 pts), confirmed in trans with a pathogenic variant (c.967G>T p.(Glu323Ter), 1.0 pt, PMID: 17318636), and confirmed in trans with two variants not yet curated by the VCEP and considered VUS (0.5 pts) (PM3_Strong).

Curation History

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