The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000070.2(CAPN3):c.223dup

Version: 1.1

CA220346

92411 (ClinVar)

Gene: DYSF (HGNC:8291)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 87928b1c-f1fb-4823-bed7-a7d20c0f6cf4
Approved on: 2025/1/7
Published on: 2025/1/7

HGVS expressions

NM_000070.2(CAPN3):c.223dup
NC_000015.10:g.42360028dup
CM000677.2:g.42360028dup
NC_000015.9:g.42652226dup
CM000677.1:g.42652226dup
NC_000015.8:g.40439518dup
NG_008660.1:g.16926dup
ENST00000349748.8:c.223dup
ENST00000357568.8:c.223dup
ENST00000397163.8:c.223dup
ENST00000466369.5:n.540+5575dup
ENST00000483208.5:n.540+5575dup
ENST00000495723.1:n.540+5575dup
ENST00000549793.5:n.540+5575dup
ENST00000318023.11:c.223dup
ENST00000349748.7:c.223dup
ENST00000357568.7:c.223dup
ENST00000397163.7:c.223dup
NM_000070.2:c.223dup
NM_024344.1:c.223dup
NM_173087.1:c.223dup
NM_000070.3:c.223dup
NM_024344.2:c.223dup
NM_173087.2:c.223dup

Pathogenic

Met criteria codes 4

PVS1 PM3_Supporting PP4 PM2_Supporting

Not Met criteria codes 19

PM6 PM1 PM5 PM4 BA1 BS1 BS3 BS2 BP5 BP7 BP4 BP3 BP1 PS1 PS2 PS3 PS4 PP2 PP3

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 Links 0

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.223dup p.(Tyr75LeufsTer5) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 1/24, leading to nonsense mediated decay in a gene in which loss of function is an established disease mechanism (PVS1). This variant has been detected in at least four individuals with LGMD (PMID: 27854218, 30564623; LOVD CAPN3_000537). In at least one case, the variant was identified in unknown phase with a pathogenic variant (c.2362_2363delinsTCATCT p.(Arg788fsTer14), 0.5 pts, LOVD Individual #00220184) (PM3_Supporting), and at least one patient with this variant displayed progressive limb girdle muscle weakness (PP4). This variant is absent from gnomAD v2.1.1 and v3.1.2 (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; 01/07/2025): PVS1, PM3_Supporting, PP4, PM2_Supporting.

Met criteria codes

PVS1	✔	The c.223dup p.(Tyr75LeufsTer5) variant in CAPN3 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 1/24 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3_Supporting	✔	This variant has been detected in at least four individuals with LGMD (PMID: 27854218, 30564623; LOVD CAPN3_000537). In at least one case, the variant was identified in unknown phase with a pathogenic variant (c.2362_2363delinsTCATCT p.(Arg788fsTer14), 0.5 pts) (PM3_Supporting).
PP4	✔	At least one patient with this variant displayed progressive limb girdle muscle weakness (PP4).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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