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Variant: NM_000070.3(CAPN3):c.1194-2A>G

Version: 1.0

CA391999297

973317 (ClinVar)

Gene: CAPN3 (HGNC:825)
Condition: autosomal recessive limb-girdle muscular dystrophy (MONDO:0015152)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8811edc5-3569-4a44-8bc0-c60e7ab6a0d9
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HGVS expressions

NM_000070.3:c.1194-2A>G
NM_000070.3(CAPN3):c.1194-2A>G
NC_000015.10:g.42399490A>G
CM000677.2:g.42399490A>G
NC_000015.9:g.42691688A>G
CM000677.1:g.42691688A>G
NC_000015.8:g.40478980A>G
NG_008660.1:g.56388A>G
ENST00000349748.8:c.1050-2A>G
ENST00000357568.8:c.1194-2A>G
ENST00000397163.8:c.1194-2A>G
ENST00000466369.5:n.1703-2A>G
ENST00000483208.5:n.1425-2A>G
ENST00000495723.1:n.1425-2A>G
ENST00000549793.5:n.1425-2A>G
ENST00000638141.2:n.1065-2A>G
ENST00000673658.1:n.178-2A>G
ENST00000673705.1:c.149-2A>G
ENST00000318023.11:c.1050-2A>G
ENST00000349748.7:c.1050-2A>G
ENST00000357568.7:c.1194-2A>G
ENST00000397163.7:c.1194-2A>G
NM_000070.2:c.1194-2A>G
NM_024344.1:c.1194-2A>G
NM_173087.1:c.1050-2A>G
NM_024344.2:c.1194-2A>G
NM_173087.2:c.1050-2A>G

Pathogenic

Met criteria codes 5

PM3 PS2_Supporting PP4_Strong PVS1 PM2_Supporting

Not Met criteria codes 1

PS1

Expert Panel

Limb Girdle Muscular Dystrophy VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Limb Girdle Muscular Dystrophy Expert Panel Specifications to the ACMG/AMP*

Evidence Links 0

Variant Interpretation Guidelines for CAPN3 Version 2.0.0

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Limb Girdle Muscular Dystrophy VCEP

The NM_000070.3: c.1194-2A>G variant in CAPN3 occurs within the canonical splice acceptor site of intron 9. This variant is predicted to abolish the consensus splice acceptor site, with a SpliceAI score of 0.99, and strengthen two alternative acceptor sites in exon 10 at +13 and +37 (SpliceAI score 0.66 and 0.36). Skipping of exon 10, which is out of frame, would be expected to disrupt the reading frame, leading to nonsense mediated RNA decay in a gene in which loss of function is an established mechanism of disease. Use of either of the alternative acceptor sites would also be expected to disrupt the reading frame (PVS1). This variant has been detected in one individual with features consistent with LGMD, where it was confirmed in trans with a pathogenic variant (c.1524G>A p.(Glu508=), 1.0 pt, ClinVar SCV001423801.2 internal data communication; PM3). This individual had a clinical diagnosis of muscular dystrophy and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (PP4_Strong). In this individual, the variant was identified as a de novo occurrence, and parental relationships were confirmed (PS2_Supporting). This variant is not found in 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 2.0.0; 10/09/2025): PVS1, PM3, PP4_Strong, PS2_Supporting, PM2_Supporting.

Met criteria codes

PM3 ✔	This variant has been detected in one individual with features consistent with LGMD, where it was confirmed in trans with a pathogenic variant (c.1524G>A p.(Glu508=), 1.0 pt, ClinVar SCV001423801.2 internal data communication; PM3). Nothing in LOVD, no other submitters in ClinVar, no lit citations in ClinVar
PS2_Supporting ✔	This variant was identified as a de novo occurrence in one patient meeting criteria for PP4, with confirmed parental relationships (ClinVar SCV001423801.2 internal data communication; PS2_Supporting).
PP4_Strong ✔	At least one patient with this variant and a second CAPN3 variant had a clinical diagnosis of muscular dystrophy and absent calpain-3 protein expression in skeletal muscle, which is highly specific for CAPN3-related LGMD (ClinVar SCV001423801.2 internal data communication; PP4_Strong). Illumina case: One patient with severe muscular dystrophy, high CPK levels, achilles tendon retractions, sural muscle hypertrophy, bilateral palpebral ptosis, severe dystrophic pattern on muscle biopsy, Muscle biopsy absent for Calpain protein.
PVS1 ✔	The NM_000070.3: c.1194-2A>G variant in CAPN3 occurs within the canonical splice acceptor site of intron 9. This variant is predicted to abolish the consensus splice acceptor site, with a SpliceAI score of 0.99, and strengthen two alternative acceptor sites in exon 10 at +13 and +37 (SpliceAI score 0.66 and 0.36). Skipping of exon 10, which is out of frame, would be expected to disrupt the reading frame, leading to nonsense mediated RNA decay in a gene in which loss of function is an established mechanism of disease. Use of either of the alternative acceptor sites would also be expected to disrupt the reading frame (PVS1). SpliceAI: acceptor loss: 0.99, skipping of exon 10 is out of frame, occurs in 35 samples in SpliceVault acceptor gain at +13: 0.66 (ref 0): out of frame, occurs in 6 samples in SpliceVault acceptor gain at +37: 0.36 (ref 0.01): out of frame, occurs in 8 samples in SpliceVault
PM2_Supporting ✔	Variant not found in gnomAD v 4.1.0 (PM2_Supporting).

Not Met criteria codes

PS1	ℹ	✖	c.1194-2del has same predicted splice effects with similar prediction scores; if LP, PS1 N/A but if P, PS1 (per Walker et al. guidelines)

Curation History

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