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Variant: NM_001100.4(ACTA1):c.1106C>T (p.Pro369Leu)

Version: 1.0

CA345144203

431989 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: bd4a8da3-d9de-4cda-9c13-1804ac87b583
Approved on: 2024/8/27
Published on: 2025/1/3

HGVS expressions

NM_001100.4:c.1106C>T
NM_001100.4(ACTA1):c.1106C>T (p.Pro369Leu)
NC_000001.11:g.229431527G>A
CM000663.2:g.229431527G>A
NC_000001.10:g.229567274G>A
CM000663.1:g.229567274G>A
NC_000001.9:g.227633897G>A
NG_006672.1:g.7570C>T
ENST00000366683.4:c.1028C>T
ENST00000684723.1:c.971C>T
ENST00000366683.3:c.737C>T
ENST00000366684.7:c.1106C>T
NM_001100.3:c.1106C>T

Pathogenic

Met criteria codes 6

PP1 PP2 PP3 PP4_Strong PM2_Supporting PS4_Moderate

Not Met criteria codes 4

BA1 BS1 BP4 BP1

Evidence Links 0

Expert Panel

Congenital Myopathies VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACTA1 Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Congenital Myopathies VCEP

The c.1106C>T (p.Pro369Leu) variant in ACTA1 is a missense variant predicted to cause substitution of proline by leucine at amino acid 369. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.922, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). ACTA1, in which the variant was identified, is defined by the ClinGen Congenital Myopathies VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant has been reported in 4 probands with nemaline myopathy, 1

with nemaline rods (PS4_Moderate; PMIDs: 19562689, 26172852; ClinVar SCVs: SCV000589626.2, SCV002287790.1; Internal lab contributors: GeneDx, Invitae). At least one patient with this variant displayed nemaline rods and type 1 fiber predominance, which is highly specific for alpha-actinopathy (PP4_Moderate, PMID: 26172852). The variant has been reported to segregate with autosomal dominant nemaline myopathy in 3 affected family members from 1 family (PP1; ClinVar SCV: SCV000589626.2, Internal lab contributors: GeneDx). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PP4_Strong, PS4_Moderate, PM2_Supporting, PP1, PP2, PP3. (Congenital Myopathies VCEP specifications version 2; 08/27/2024)

Met criteria codes

PP1	✔	The variant has been reported to segregate with nemaline myopathy in 3 affected family members from 1 family (PP1; GeneDx).
PP2	✔	ACTA1, in which the variant was identified, is defined by the ClinGen Congenital Myopathies VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3	✔	The computational predictor REVEL gives a score of 0.922, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PP4_Strong	✔	At least one patient with this variant displayed nemaline rods and type 1 fiber predominance, which is highly specific for alpha-actinopathy. This patient had comprehensive genetic testing; therefore PP4 was upgraded to Strong (PP4_Strong, PMID: 26172852).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Moderate	✔	This variant has been reported in 4 probands with nemaline myopathy, 1 with nemaline rods (PS4_Moderate; PMIDs: 19562689, 26172852; ClinVar SCVs: SCV000589626.2, SCV002287790.1; Internal lab contributors: GeneDx, Invitae).

Not Met criteria codes

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
BP4	✖	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

Curation History

Showing 1 to 1 of 1 rows

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