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_001100.4(ACTA1):c.1001C>T (p.Pro334Leu)

Version: 1.1

CA345144967

532770 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 8f17182e-ef54-4e16-b059-5371047530b0
Approved on: 2024-09-09
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HGVS expressions

NM_001100.4:c.1001C>T
NM_001100.4(ACTA1):c.1001C>T (p.Pro334Leu)
NC_000001.11:g.229431632G>A
CM000663.2:g.229431632G>A
NC_000001.10:g.229567379G>A
CM000663.1:g.229567379G>A
NC_000001.9:g.227634002G>A
NG_006672.1:g.7465C>T
ENST00000366683.4:c.991-68C>T
ENST00000684723.1:c.866C>T
ENST00000366683.3:c.632C>T
ENST00000366684.7:c.1001C>T
NM_001100.3:c.1001C>T

Likely Pathogenic

Met criteria codes 6

PS4_Moderate PM5_Supporting PM2_Supporting PP4_Moderate PP2 PP3

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.1001C>T (NM_001100.4(ACTA1):c.1001C>T (p.Pro334Leu)) variant in ACTA1 is a missense variant predicted to cause substitution of proline by leucine at amino acid 334 (p.Pro334Leu). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.814, 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). Another missense variant

p.Pro334Arg (c.1001C>G) [ClinVar Variation ID: 1031829] in the same codon has been classified as likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5_supporting). This variant has been identified in 4 probands with autosomal dominant alpha-actinopathy. At least one patient with this variant displayed rods on a muscle biopsy, which is highly specific for alpha-actinopathy (PS4_moderate, PP4_moderate; Invitae, Paris-East Créteil University internal data, Alan Beggs personal communication, LOVD). Of note, all probands displayed later than typical onset of symptoms with onset ranging from late teens to the 5th or 6th decade of life. In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PM2_supporting, PP3, PP2, PM5_supporting, PS4_moderate, PP4_moderate (ClinGen Congenital Myopathies VCEP Specifications Version 2.0; 9/9/2024).

Met criteria codes

PS4_Moderate	✔	This variant has been reported in 6 probands with features consistent with alpha-actinopathy (PS4_moderate; SCVs: SCV003822533, SCV001746905, SCV000761247; Laboratories: Revvity Omics, Paris-East Créteil University (UPEC), CeGaT, Invitae, Alan Beggs personal communication, LOVD).
PM5_Supporting	✔	Another missense variant p.Pro334Arg (c.1001C>G) [ClinVar Variation ID: 1031829] in the same codon has been classified as likely pathogenic for actin accumulation myopathy by the ClinGen Congenital Myopathies VCEP (PM5_supporting).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage is adequate for this region of the gene.
PP4_Moderate	✔	At least one patient with this variant displayed rods on a muscle biopsy, which is highly specific for actin accumulation myopathy (PP4_moderate; Invitae internal data & Revvity Omics Internal Data).
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). The gnomAD v4.1.0 Z score for missense variants is 6.09.
PP3	✔	The computational predictor REVEL gives a score of 0.814, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). The UCSC Genome Browser indicates high conservation of this residue. The majority of in-silico predictors support a deleterious effect of this variant on protein function.

Curation History

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