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# *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**: 2024/9/9
**Published on**: 2025/4/2

## *HGVS expressions*

**NM_001100.4(ACTA1):c.1001C>T (p.Pro334Leu)**
**NM_001100.4:c.1001C>T**
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

PM2_Supporting | PP2 | PP3 | PS4_Moderate | PP4_Moderate | PM5_Supporting

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**

| | | |
|---|---|---|
| **PM2_Supporting** | ✔ | This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage is adequate for this region of the gene. |
| **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. |
| **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). |
| **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). |
| **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). |

Curation History

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