

Variant: NM_001100.4(ACTA1):c.1000C>T (p.Pro334Ser)

Version: 1.1

CA341499 [↗](#)

18291 (ClinVar) [↗](#)

Gene: ACTA1 ([HGNC:58](#))

Condition: alpha-actinopathy ([MONDO:0100084](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 0700c61d-d15f-4e6d-b5eb-4aacac32eeb5

Approved on: 2024/10/25

Published on: 2025/4/2

HGVS expressions

NM_001100.4(ACTA1):c.1000C>T (p.Pro334Ser)

NM_001100.4:c.1000C>T

NC_000001.11:g.229431633G>A

CM000663.2:g.229431633G>A

NC_000001.10:g.229567380G>A

CM000663.1:g.229567380G>A

NC_000001.9:g.227634003G>A

NG_006672.1:g.7464C>T

ENST00000366683.4:c.991-69C>T

ENST00000684723.1:c.865C>T

ENST00000366683.3:c.631C>T

ENST00000366684.7:c.1000C>T

NM_001100.3:c.1000C>T

Pathogenic

Met criteria codes **6**

PM5

PS3

PM2_Supporting

PP2

PP3

PP4

Evidence Links **1**

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.1000C>T (NM_001100.4(ACTA1):c.1000C>T (p.Pro334Ser)) variant in ACTA1 is a missense variant predicted to cause substitution of proline by serine at amino acid 334 (p.Pro334Ser). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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 computational predictor REVEL gives a score of 0.919, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). 2 different missense variants,

[p.Pro334Leu, (VCV000532770); p.Pro334Arg, (VCV001031829)], in the same codon have been classified as likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5). One patient with the p.Pro334Ser variant displayed fiber type disproportion, which is highly specific for alpha-actinopathy (PP4, PMID: 15468086 & University of Western Australia internal data). Localization analysis of the mutant in myotubes showed no incorporation into nascent sarcomeres. Analysis in fibroblasts showed diffuse cytoplasmic myc-actin staining (PMID: 19206168; PS3). 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: PM2_supporting, PP2, PP3, PM5, PP4, PS3 (ClinGen Congenital Myopathies VCEP Specifications Version 2.0; 10/25/24).

Met criteria codes

PM5			2 different missense variants, [p.Pro334Leu, (VCV000532770); p.Pro334Arg, (VCV001031829)], in the same codon have been classified as likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5).
PS3			Localization analysis of the mutant in myotubes showed no incorporation into nascent sarcomeres. Analysis in fibroblasts showed diffuse cytoplasmic myc-actin staining (PMID: 19206168; PS3). Code is applied at the strong level due to evidence in two different cell types and specificity of evidence. Localization: 85 % of fibroblasts with p.Pro334Ser mutant have a diffuse cytoplasmic localization of actin have a diffuse cytoplasmic localization, and only partially incorporate into actin filaments. In the myotube analysis, there was no incorporation into nascent sarcomeres. PubMed:19206168 
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the gene in the region this variant is found is adequate.
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). ACTA1 has a Z-score of 6.09 for missense variants.
PP3			The computational predictor REVEL gives a score of 0.919, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PP4			One patient with this variant displayed fiber type disproportion, which is highly specific for alpha-actinopathy (PP4, PMID: 15468086 & University of Western Australia internal data).

Curation History 



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