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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

PM2_Supporting PP2 PP3 PP4 PM5 PS3

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

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).
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**

Curation History

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