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Variant: NM_001100.4(ACTA1):c.1001C>G (p.Pro334Arg)

Version: 1.0

CA345144971

1031829 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 1348c9f8-dc41-4610-b7d0-919a1b090307
Approved on: 2024/8/27
Published on: 2025/1/3

HGVS expressions

NM_001100.4(ACTA1):c.1001C>G (p.Pro334Arg)
NM_001100.4:c.1001C>G
NC_000001.11:g.229431632G>C
CM000663.2:g.229431632G>C
NC_000001.10:g.229567379G>C
CM000663.1:g.229567379G>C
NC_000001.9:g.227634002G>C
NG_006672.1:g.7465C>G
ENST00000366683.4:c.991-68C>G
ENST00000684723.1:c.866C>G
ENST00000366683.3:c.632C>G
ENST00000366684.7:c.1001C>G
NM_001100.3:c.1001C>G

Pathogenic

Met criteria codes 6

PM2_Supporting PP2 PP3 PM5 PS4_Supporting PS2

Not Met criteria codes 1

PS3

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>G variant in ACTA1 is a missense variant predicted to cause a substitution of proline by arginine at amino acid position 334. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.893, which is above the threshold of 0.7 set by the CM VCEP (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 identified as a de novo occurrence with confirmed parental relationships in one individual and as a de

novo occurrence with unconfirmed parental relationships in one individual with alpha-actinopathy (PS4_Supporting, PS2; Invitae internal data; PMID: 19562689,). Another missense variant c.1000C>T, p.Pro334Ser (PMID: 15468086) in the same codon has been classified as likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5). 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:PS2, PM5, PS4_Supporting, PM2_Supporting, PP2, PP3 (Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v 4.1.0 (PM2_Supporting).
PP2	✔	ACTA1, in which the variant was identified, is defined by the ClinGen CM 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). gnomAD Z score = 6.09
PP3	✔	The computational predictor REVEL gives a score of 0.893, which is above the threshold of 0.75, evidence that correlates with impact to ACTA1 function (PP3).
PM5	✔	Another missense variant c.1000C>T, p.Pro334Ser (PMID: 15468086) in the same codon has been classified as likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5).
PS4_Supporting	✔	The p.Pro334Arg variant was identified as a de novo observation in one individual with nemaline myopathy requested (NMR) (PMID: 19562689). This variant was also reported in an individual with congenital myopathy, severe hypotonia, and stridor/respiratory distress (Invitae internal data; PS4_Supporting).
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in one individual and as a de novo occurrence with unconfirmed parental relationships in one individual with congenital myopathy (PS2; Invitae internal data; PMID: 19562689,).

Not Met criteria codes

PS3	✖	To our knowledge, functional assays have not been reported for this variant.

Curation History

Showing 1 to 1 of 1 rows

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