

Variant: *NM_001100.4(ACTA1):c.304G>A (p.Glu102Lys)*

Version: 1.1

CA16603574 [↗](#)

377433 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 87018d01-b34d-4728-a771-c1f796dfaf59

Approved on: 2024/9/9

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HGVS expressions

NM_001100.4:c.304G>A

NM_001100.4(ACTA1):c.304G>A (p.Glu102Lys)

NC_000001.11:g.229432706C>T

CM000663.2:g.229432706C>T

NC_000001.10:g.229568453C>T

CM000663.1:g.229568453C>T

NC_000001.9:g.227635076C>T

NG_006672.1:g.6391G>A

ENST00000366683.4:c.304G>A

ENST00000684723.1:c.169G>A

ENST00000366683.3:c.304G>A

ENST00000366684.7:c.304G>A

NM_001100.3:c.304G>A

Likely Pathogenic

Met criteria codes **6**

PM2_Supporting

PP4_Moderate

PS4_Moderate

PP1

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.304G>A (NM_001100.4(ACTA1):c.304G>A (p.Glu102Lys)) variant in ACTA1 is a missense variant predicted to cause substitution of glutamate by lysine at amino acid 102 (p.Glu102Lys). 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 0.854, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). This variant has been reported in

4 probands with alpha-actinopathy (PS4_Moderate; SCV000511956, SCV003347757; Invitae & GeneDx Internal Data). At least one patient with this variant displayed muscle biopsy with fiber type disproportion, which is highly specific for alpha-actinopathy (PP4_Moderate; SCV003347757, Invitae internal data). The variant has been reported to segregate with alpha-actinopathy in one affected daughter (PP1; SCV003347757, Invitae internal data). 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, PP2, PP3, PS4_Moderate, PP4_Moderate, PP1 (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 of ACTA1 in the region in which this variant is found is adequate.
PP4_Moderate			At least one patient with this variant displayed muscle biopsy with fiber type disproportion, which is highly specific for alpha-actinopathy (PP4_moderate; SCV003347757, Invitae internal data).
PS4_Moderate			This variant has been reported in 5 probands from 4 families with alpha-actinopathy (PS4_moderate).
PP1			The variant has been reported to segregate with alpha-actinopathy in one affected daughter (PP1; SCV003347757, Invitae 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 is 6.09.
PP3			The computational predictor REVEL gives a score of 0.854, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).

Curation History

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