

Variant: *NM_001100.4(ACTA1):c.283G>A (p.Glu95Lys)*

Version: 1.0

CA345150112 [↗](#)

654469 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 813ff07f-556e-4768-9347-9b93e3c210dd

Approved on: 2024/8/27

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HGVS expressions

NM_001100.4(ACTA1):c.283G>A (p.Glu95Lys)

NM_001100.4:c.283G>A

NC_000001.11:g.229432727C>T

CM000663.2:g.229432727C>T

NC_000001.10:g.229568474C>T

CM000663.1:g.229568474C>T

NC_000001.9:g.227635097C>T

NG_006672.1:g.6370G>A

ENST00000366683.4:c.283G>A

ENST00000684723.1:c.148G>A

ENST00000366683.3:c.283G>A

ENST00000366684.7:c.283G>A

NM_001100.3:c.283G>A

Pathogenic

Met criteria codes 6

PM2_Supporting

PS4_Moderate

PS2_Supporting

PP2

PP3

PP4_Strong

Not Met criteria codes 4

BA1

BP4

BP1

BS1

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.283G>A variant in ACTA1 is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 95 (legacy nomenclature: p.Glu93Lys). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.933, 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). This variant has been reported in 4 probands with severe

hypotonia and/or congenital myopathy (PS4_Moderate; PMID: 35810298, Invitae, ClinVar SCV:SCV000950636.2). In one of those four individuals, the variant has been identified as a de novo occurrence with confirmed parental relationships (PS2; Invitae, ClinVar SCV:SCV000950636.2). At least one patient with this variant displayed intranuclear rods and type 1 muscle fiber predominance, which is highly specific for alpha-actinopathy and has had exome testing that is negative for all other causes of myopathy (PP4_Strong, PMID: 35810298). 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: PP4_Strong, PS4_Moderate, PS2_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 v4.1.1 (PM2_Supporting).
PS4_Moderate			4 individuals, all were infants with severe hypotonia and/or congenital myopathy (0.25 PS4 Points Each, 1 Total; PS4).
PS2_Supporting			In one individual, the variant was determined to occur de novo, parents tested and relatedness confirmed (0.5 PS2 Points, PS2_Supporting). Family testing was not performed for the remaining individuals.
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).
PP3			The computational predictor REVEL gives a score of 0.933, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PP4_Strong			At least one patient with this variant displayed intranuclear rods and type 1 muscle fiber predominance, which is highly specific for alpha-actinopathy and has had exome testing that is negative for all other causes of myopathy (PP4_Strong, PMID: 35810298).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline



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