

Variant: NM_001100.4(ACTA1):c.39C>A (p.Asp13Glu)

Version: 1.0

CA345151708 [↗](#)

951155 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: d0fccf15-f47a-4ff4-bd85-deba07e00f3f

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HGVS expressions

NM_001100.4:c.39C>A

NM_001100.4(ACTA1):c.39C>A (p.Asp13Glu)

NC_000001.11:g.229433077G>T

CM000663.2:g.229433077G>T

NC_000001.10:g.229568824G>T

CM000663.1:g.229568824G>T

NC_000001.9:g.227635447G>T

NG_006672.1:g.6020C>A

ENST00000366683.4:c.39C>A

ENST00000684723.1:c.-6-197C>A

ENST00000366683.3:c.39C>A

ENST00000366684.7:c.39C>A

NM_001100.3:c.39C>A

Likely Pathogenic

Met criteria codes **5**

PS2

PM2_Supporting

PP2

PP3

PP1_Moderate

Not Met criteria codes **2**

BA1

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

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001100.4(ACTA1):c.39C>A variant in ACTA1 is a missense variant predicted to cause a substitution of aspartate by glutamate at amino acid 13 (p.Asp13Glu). This variant is absent from gnomAD v4.1.1 (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 dominant disease (PP2). The computational predictor REVEL gives a score of 0.903, which is above the threshold of 0.7, so evidence does correlate with impact on ACTA1 function (PP3). This variant has been observed in the

heterozygous state in two individuals with progressive cardiomyopathy (requiring transplantation in one) and milder muscle weakness, one of which was confirmed de novo (PS2, PS4_Supporting; Labcorp Genetics SCV001395135.7, GeneDx SCV001823123.1). Additionally, the variant segregated with disease in two individuals from one family (PP1_Moderate). 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: PS2, PP1_Moderate, PS4_Supporting, PM2_Supporting, PP2, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2.0).

Met criteria codes

PS2			This variant has been observed as de novo in one individual with confirmed parentage (PS2; Labcorp Genetics SCV001395135.7).
PM2_Supporting			This variant is absent from gnomAD v4.1.1 meeting PM2_Supporting.
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 dominant disease
PP3			The REVEL score is 0.903, which is above the threshold of 0.7
PP1_Moderate			This variant segregated with disease in two individuals from one family (PP1_Moderate, GeneDx SCV001823123.1).

Not Met criteria codes

BA1			This variant is absent from gnomAD v4.1.1 meeting PM2_Supporting.
BS1			This variant is absent from gnomAD v4.1.1 meeting PM2_Supporting.

Curation History



 

 

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