

Variant: *NM_001100.4(ACTA1):c.1007A>C (p.Glu336Ala)*

Version: 1.1

CA128033 [↗](#)

18288 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 9148486b-0040-49d6-a7d4-c6589b4f51e8

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HGVS expressions

NM_001100.4:c.1007A>C

NM_001100.4(ACTA1):c.1007A>C (p.Glu336Ala)

NC_000001.11:g.229431626T>G

CM000663.2:g.229431626T>G

NC_000001.10:g.229567373T>G

CM000663.1:g.229567373T>G

NC_000001.9:g.227633996T>G

NG_006672.1:g.7471A>C

ENST00000366683.4:c.991-62A>C

ENST00000684723.1:c.872A>C

ENST00000366683.3:c.638A>C

ENST00000366684.7:c.1007A>C

NM_001100.3:c.1007A>C

Likely Pathogenic

Met criteria codes 5

PP1_Moderate

PP4_Moderate

PP2

PP3

PM2_Supporting

Not Met criteria codes 1

PS4

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.1007A>C (NM_001100.4(ACTA1):c.1007A>C (p.Glu336Ala)) variant in ACTA1 is a missense variant predicted to cause substitution of glutamate by alanine at amino acid 336 (p.Glu336Ala). 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 0.874, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). At least one patient with this

variant displayed cores and fiber type disproportion on muscle biopsy, which is highly specific for actin accumulation myopathy (PP4_Moderate, PMID: 15520409). This variant has been reported in 5 individuals from one family with muscle weakness (PP1_Moderate; PMID: 15520409). 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, PP4_Moderate, PP1_Moderate (Congenital Myopathies VCEP Specifications Version 2.0; July 8, 2024).

Met criteria codes

PP1_Moderate			This variant has been reported in 5 individuals from one family with muscle weakness (PP1_moderate; PMID: 15520409).
PP4_Moderate			At least one patient with this variant displayed cores and fiber type disproportion on muscle biopsy, which is highly specific for actin accumulation myopathy (PP4_moderate, PMID: 15520409).
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). Z-score for missense variants in this gene is 6.09.
PP3			The computational predictor REVEL gives a score of 0.874, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting). Coverage of the gene in the region within which the variant is found is adequate.

Not Met criteria codes

PS4			This variant has been reported in 5 probands from one family with muscle weakness (No case codes met; PMID: 15520409).
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Curation History



 

 

Showing 1 to 2 of 2 rows

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