The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2024/7/8
Published on: 2025/4/2

HGVS expressions

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

PM2_Supporting PP2 PP3 PP4_Moderate PP1_Moderate

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

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.
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).
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).
PP1_Moderate	✔	This variant has been reported in 5 individuals from one family with muscle weakness (PP1_moderate; PMID: 15520409).

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).

Curation History

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.