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.172G>A (p.Asp58Asn)

Version: 1.0

CA345150874

427190 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: c6230021-44c3-448a-9d24-ff554c173be1
Approved on: 2024-08-27
Published on: 2025-01-03

HGVS expressions

NM_001100.4:c.172G>A
NM_001100.4(ACTA1):c.172G>A (p.Asp58Asn)
NC_000001.11:g.229432838C>T
CM000663.2:g.229432838C>T
NC_000001.10:g.229568585C>T
CM000663.1:g.229568585C>T
NC_000001.9:g.227635208C>T
NG_006672.1:g.6259G>A
ENST00000366683.4:c.172G>A
ENST00000684723.1:c.37G>A
ENST00000366683.3:c.172G>A
ENST00000366684.7:c.172G>A
NM_001100.3:c.172G>A

Likely Pathogenic

Met criteria codes 4

PS2 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.172G>A variant in ACTA 1 is a missense variant predicted to cause a substitution of aspartic acid by asparagine at amino acid position 58. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.893, which is above the threshold of 0.7 set by the CM VCEP (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 was observed to occur de novo in a proband with congenital hypotonia, muscle weakness, failure

to thrive, poor feeding, developmental delay and normal creatine kinase levels (PS2, SCV000934090.3). 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, PM2_Supporting, PP2, PP3 (Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PS2	✔	This variant was observed to occur de novo in a proband with congenital hypotonia, muscle weakness, failure to thrive, poor feeding, developmental delay and normal creatine kinase levels (PS2, Invitae internal data, SCV000934090.3).
PP2	✔	ACTA1, in which the variant was identified, is defined by the ClinGen CM 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). gnomAD Z score = 6.09
PP3	✔	The computational predictor REVEL gives a score of 0.893, which is above the threshold of 0.75
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.1 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant was observed to occur de novo in a proband with congenital hypotonia, muscle weakness, failure to thrive, poor feeding, developmental delay and normal creatine kinase levels (SCV000934090.3).

Curation History

Showing 1 to 1 of 1 rows