

Variant: NM_001100.4(ACTA1):c.868G>C (p.Asp290His)

Version: 1.0

CA345145962 [↗](#)

521371 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: da8a4820-72dd-4373-bc1d-ec60f9fde1e8

Approved on: 2024/8/27

Published on: 2024/12/12

HGVS expressions

NM_001100.4(ACTA1):c.868G>C (p.Asp290His)

NM_001100.4:c.868G>C

NC_000001.11:g.229431843C>G

CM000663.2:g.229431843C>G

NC_000001.10:g.229567590C>G

CM000663.1:g.229567590C>G

NC_000001.9:g.227634213C>G

NG_006672.1:g.7254G>C

ENST00000366683.4:c.868G>C

ENST00000684723.1:c.733G>C

ENST00000366683.3:c.499G>C

ENST00000366684.7:c.868G>C

NM_001100.3:c.868G>C

Pathogenic

Met criteria codes **7**

PS2

PM5

PM2_Supporting

PP2

PP3

PP4_Moderate

PS4_Supporting

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.868G>C variant in ACTA1 is a missense variant predicted to cause substitution of aspartic acid by histidine at amino acid 290 (legacy nomenclature: p.Asp288His). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.985, 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 2 probands ,

including one with a muscle biopsy containing nemaline rods (PS4_Supporting, PP4_Moderate; PMIDs: 29565416, 28516742). In both individuals, the variant has been identified as a de novo occurrence with confirmed parental relationships (PS2). Another missense variant c.868G>A, p.Asp290Asn (PMIDs: 19562689, 27242277) in the same codon has been classified as pathogenic for AD nemaline myopathy by the ClinGen Congenital Myopathies VCEP (PM5). 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: PS2, PM5, PP4_Moderate, PS4_Supporting, PM2_Supporting, PP2, PP3 (Congenital Myopathies VCEP specifications version 1; 08/27/2024).

Met criteria codes

PS2			The p.Asp290His variant was identified as a de novo observation in two individuals, both with parental relationships confirmed by WES (PMID: 29565416, 28516742). One did not have specific phenotypes detailed and the other had Nemaline rods present in biopsy, which is highly specific for ACTA1 variants.
PM5			Another missense variant c.868G>A, p.Asp290Asn (PMIDs: 19562689, 27242277) in the same codon has been classified as pathogenic for AD nemaline myopathy by the ClinGen Congenital Myopathies VCEP (PM5).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
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 4.1.0 Z score = 6.09
PP3			The computational predictor REVEL gives a score of 0.985, which is above the threshold of 0.75, evidence that correlates with impact to ACTA1 function (PP3).
PP4_Moderate			This variant has been reported in 2 probands , including one with a muscle biopsy containing nemaline rods (PS4_Supporting, PP4_Moderate; PMIDs: 29565416, 28516742).
PS4_Supporting			The p.Asp290His variant was identified as a de novo observation in one individual without specific phenotypes provided. (PMID:29565416) and a second infant with nemaline rods confirmed on biopsy (PMID: 28516742).

Curation History



 

 

Showing 1 to 1 of 1 rows

--

