

Variant: *NM_001100.4(ACTA1):c.493G>A (p.Val165Met)*

Version: 1.0

CA258144 [↗](#)

18292 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: dafe07a8-2578-4074-8f38-bad29ef7c164

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HGVS expressions

NM_001100.4:c.493G>A

NM_001100.4(ACTA1):c.493G>A (p.Val165Met)

NC_000001.11:g.229432393C>T

CM000663.2:g.229432393C>T

NC_000001.10:g.229568140C>T

CM000663.1:g.229568140C>T

NC_000001.9:g.227634763C>T

NG_006672.1:g.6704G>A

ENST00000366683.4:c.493G>A

ENST00000684723.1:c.358G>A

ENST00000366683.3:c.479+14G>A

ENST00000366684.7:c.493G>A

NM_001100.3:c.493G>A

Pathogenic

Met criteria codes 6

PP1_Moderate

PS3

PP2

PP3

PM2_Supporting

PP4_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.493G>A variant in ACTA1 is a missense variant predicted to cause substitution of valine by methionine at amino acid 165 (legacy nomenclature: p.Val163Met). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.961, 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). In vitro studies in C2C12 myoblasts showed that

V165M formed intranuclear actin aggregates with low levels of cytoplasmic aggregates, indicating that this variant impacts protein function. These oblong intranuclear aggregates closely resembled intranuclear bodies observed in muscle samples from patients with intranuclear myopathy. Additionally, Drosophila heterozygous for V165M show that V165M can severely affect Z-disc assembly and the stability of the sarcomere. Heterozygous V165M Drosophila presented with zebra bodies, Z-rings, and intranuclear rods (PS3; PMID:15198992, 17705262, 23294764). This variant has been reported in 1 proband with intranuclear rod myopathy confirmed by biopsy (PP4_Moderate; PMID:12921789). The variant has been reported to segregate with nemaline myopathy in 2 affected family members from 1 family (PP1_Moderate; PMID: 12921789). 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: PS3, PP4_Moderate, PP1_Moderate, PM2_Supporting, PP3, PP2 (Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PP1_Moderate			The variant has been reported to segregate with nemaline myopathy in 2 affected family members from 1 family (PP1_Moderate; PMID: 12921789).
PS3			In vitro studies in C2C12 myoblasts showed that V165M formed intranuclear actin aggregates with low levels of cytoplasmic aggregates, indicating that this variant impacts protein function. These oblong intranuclear aggregates closely resembled intranuclear bodies observed in muscle samples from patients with intranuclear myopathy. Additionally, Drosophila heterozygous for V165M show that V165M can severely affect Z-disc assembly and the stability of the sarcomere. Heterozygous V165M Drosophila presented with zebra bodies, Z-rings, and intranuclear rods (PS3; PMID:15198992, 17705262, 23294764).
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). (gnomAD 4.1.0 z=6.09)
PP3			The computational predictor REVEL gives a score of 0.961, 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).
PP4_Moderate			This variant has been reported in 1 proband with intranuclear rod myopathy with muscle biopsy with Intranuclear rods (PP4_Moderate; PMID:12921789).

Not Met criteria codes

PS4			This variant has been reported in 1 proband with intranuclear rod myopathy (PS4; PMID:12921789).
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Curation History 

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