

Variant: *NM_001100.4(ACTA1):c.541del (p.Asp181fs)*

Version: 1.0

CA1442845 [↗](#)

420100 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: b0b43b29-0998-4f68-992c-a07ff5a3d9a6

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HGVS expressions

NM_001100.4:c.541del

NM_001100.4(ACTA1):c.541del (p.Asp181fs)

NC_000001.11:g.229432346del

CM000663.2:g.229432346del

NC_000001.10:g.229568093del

CM000663.1:g.229568093del

NC_000001.9:g.227634716del

NG_006672.1:g.6752del

ENST00000366683.4:c.541del

ENST00000684723.1:c.406del

ENST00000366683.3:c.479+62del

ENST00000366684.7:c.541del

NM_001100.3:c.541del

Pathogenic

Met criteria codes 4

PVS1

PS3_Supporting

PP4_Moderate

PM3

Not Met criteria codes 3

BS1

BA1

PM2

Evidence Links 1

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 1.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001100.4:c.541del (p.Asp181fs) variant in ACTA1 is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 4/7 and to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The highest population filtering allele frequency in gnomAD v4.1 is 0.0002402 (29/91056 alleles) in the South Asian population (this variant is excluded from the application of BA1/BS1 by the ClinGen Congenital Myopathies VCEP as it is a well established pathogenic variant). This variant has been detected in 6 individuals with nemaline myopathy. All of these individuals were homozygous for the variant

(PMID: 17187373, GeneDx, SCV000568673.4) (PM3). Multiple patients with this variant displayed zebra bodies, which is highly specific for nemaline myopathy (PP4, PMID: 17187373). Western blot analysis of the muscle biopsy in one of the patients showed complete absence of α -skeletal muscle actin, whereas they had high levels of α -cardiac actin when compared with control subjects indicating that this variant impacts protein expression (PMID: 17187373) (PS3_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PVS1, PM3, PS3_Supporting, PP4 (ClinGen Congenital Myopathies VCEP specifications version 1; 08/07/2024).

Met criteria codes

PVS1			The c.541del (p.Asp181fs) variant in ACTA1 is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 4/7 is predicted to lead to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PS3_Supporting			Western blot analysis of the muscle biopsy in Patient 3 showed complete absence of α -skeletal muscle actin, whereas they had high levels of α -cardiac actin when compared with control subjects indicating that this variant impacts protein function (PMID: 17187373)(PS3_Supporting).
			Western blot analysis of the muscle biopsy in Patient 3 showed complete absence of α -skeletal muscle actin, whereas they had high levels of α -cardiac actin when compared with control subjects indicating that this variant impacts protein function (PMID: 17187373)(PS3_Supporting). PubMed:17187373 
PP4_Moderate			Multiple patients with this variant displayed zebra bodies, which is highly specific for nemaline myopathy (PP4, PMID: 17187373).
PM3			This variant has been detected in 6 individuals with nemaline myopathy. All individuals were homozygous for the variant (PM3, PMID: 17187373, GeneDx, SCV000568673.4). Heterozygous parents were unaffected.

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			The highest population filtering allele frequency in gnomAD v4.1 is 0.0002402 (29/91056 alleles) in the South Asian population (BA1 is not met as this variant is excluded).
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 

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