

Variant: NM_001100.4(ACTA1):c.109G>T (p.Val37Leu)

Version: 1.0

CA345151305 [↗](#)

464114 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 1dbcbf38-ff96-4bff-a816-a36808aeb828

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HGVS expressions

NM_001100.4(ACTA1):c.109G>T (p.Val37Leu)

NM_001100.4:c.109G>T

NC_000001.11:g.229433007C>A

CM000663.2:g.229433007C>A

NC_000001.10:g.229568754C>A

CM000663.1:g.229568754C>A

NC_000001.9:g.227635377C>A

NG_006672.1:g.6090G>T

ENST00000366683.4:c.109G>T

ENST00000684723.1:c.-6-127G>T

ENST00000366683.3:c.109G>T

ENST00000366684.7:c.109G>T

NM_001100.3:c.109G>T

Pathogenic

Met criteria codes 5

PM5_Strong

PP2

PP3

PS2

PM2_Supporting

Not Met criteria codes 5

BA1

BP4

BS1

PS1

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 NM_001100.4(ACTA1):c.109G>T variant in ACTA1 is a missense variant predicted to cause substitution of valine by leucine at amino acid 37 (legacy nomenclature: p.Val35Leu). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.881, 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). Three other variants occur at the same

residue (c.110T>C (p.V37A); c.110T>G (p.V37G)) with c.109G>C (p.V37L) occurring at the same nucleotide (PM5_Strong). This variant has occurred de novo in one individual with nemaline myopathy, hypotonia, respiratory distress, and cardiac arrest (PS2; PMID:28973083, Baylor Genetics, SCV000807332.1). 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_Strong, PM2_Supporting, PP2, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PM5_Strong			Three other variants occur at the same residue (c.110T>C (p.V37A); c.110T>G (p.V37G)) with c.109G>C (p.V37L) occurring at the same nucleotide.
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).
PP3			The computational predictor REVEL gives a score of 0.881, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PS2			This variant has occurred de novo in one individual with nemaline myopathy, hypotonia, respiratory distress, and cardiac arrest (PS2 PMID:28973083, Baylor Genetics, SCV000807332.1).
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).

Not Met criteria codes

BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			Three other variants occur at the same residue (c.110T>C (p.V37A); c.110T>G (p.V37G)) with c.109G>C (p.V37L) occurring at the same nucleotide.
PS4			This variant has occurred de novo in one individual with nemaline myopathy, hypotonia, respiratory distress, and cardiac arrest (PS2; PMID:28973083, Baylor Genetics, SCV000807332.1).

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