

Variant: NM_001100.4(ACTA1):c.1043T>A (p.Leu348Gln)

Version: 1.0

CA345144656 [↗](#)

1303122 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b8aa8cd3-c0d4-4548-ac55-966ad6c57973

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HGVS expressions

NM_001100.4:c.1043T>A

NM_001100.4(ACTA1):c.1043T>A (p.Leu348Gln)

NC_000001.11:g.229431590A>T

CM000663.2:g.229431590A>T

NC_000001.10:g.229567337A>T

CM000663.1:g.229567337A>T

NC_000001.9:g.227633960A>T

NG_006672.1:g.7507T>A

ENST00000366683.4:c.991-26T>A

ENST00000684723.1:c.908T>A

ENST00000366683.3:c.674T>A

ENST00000366684.7:c.1043T>A

NM_001100.3:c.1043T>A

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PP2

PP3

PS4_Supporting

PM2_Supporting

Not Met criteria codes **16**

BP4

BP3

BP1

BP2

BP7

BS2

BS1

BS3

PS1

PS3

BA1

PM1

PM3

PM5

PM4

PVS1

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 variant NM_001100.4:c.1043T>A in ACTA1 is a missense variant predicted to cause substitution of leucine by glutamine at amino acid 348 (p.Leu348Gln). The variant is absent from gnomAD v4.1.0 with adequate coverage (PM2_Supporting). The REVEL computational prediction analysis tool gives a score of 0.976, which is above the threshold necessary to apply PP3. In addition, 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 two probands with

congenital myopathy (PS4_Supporting, PMID:25747004, SCV002280810.3). The one proband had hypotonia at birth, end stage limb-girdle dystrophy with diffuse proximal and distal weakness and wasting, and weak axial muscles. Muscle biopsy of this proband showed nemaline rods and electron microscopy showed few zebra bodies and accumulation of actin-like thin filaments (PP4_Moderate, PMID:25747004). In summary, the variant meets the criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy. ACMG/AMP criteria met, as specified by the ClinGen Congenital Myopathies VCEP: PP4_Moderate, PS4_Supporting, PP2, PP3, PM2_Supporting (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PP4_Moderate			This variant has been reported in one proband with congenital myopathy. The proband had hypotonia at birth, end stage limb-girdle dystrophy with diffuse proximal and distal weakness and wasting, and weak axial muscles. Muscle biopsy of this proband showed nemaline rods and electron microscopy showed few zebra bodies and accumulation of actin-like thin filaments (PP4_Moderate. PMID:25747004).
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). The Z-score in gnomAD 4.1.0 is 6.09.
PP3			The computational predictor REVEL gives a score of 0.976, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PS4_Supporting			This variant has been reported in one proband with congenital myopathy (PMID:25747004).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_supporting). Coverage of the gene in this region is adequate.

Not Met criteria codes

BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1			This variant is absent from gnomAD v2.1.1 with adequate coverage
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			This variant is absent from gnomAD v2.1.1 with adequate coverage
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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