

Variant: *NM_001100.4(ACTA1):c.685A>T (p.Met229Leu)*

Version: 1.0

CA345147069 [↗](#)

657321 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: bcf61e30-24d3-4a5f-8efe-b28e02c0f86f

Approved on: 2026/6/8

Published on: 2026/6/22

HGVS expressions

NM_001100.4:c.685A>T

NM_001100.4(ACTA1):c.685A>T (p.Met229Leu)

NC_000001.11:g.229432117T>A

CM000663.2:g.229432117T>A

NC_000001.10:g.229567864T>A

CM000663.1:g.229567864T>A

NC_000001.9:g.227634487T>A

NG_006672.1:g.6980A>T

ENST00000366683.4:c.685A>T

ENST00000684723.1:c.550A>T

ENST00000366683.3:c.480-255A>T

ENST00000366684.7:c.685A>T

NM_001100.3:c.685A>T

Likely Pathogenic

Met criteria codes **2**

PM2_Supporting

PP2

Not Met criteria codes **3**

BP4

BP1

PP3

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.685A>T in ACTA1 is a missense variant predicted to cause substitution of methionine by leucine at amino acid 229 (p.Met229Leu). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.617, which is neither above nor below the thresholds predicting a damaging or benign impact on ACTA1 function. 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). Six different missense variants,

[c.685A>G (p.Met229Val), c.686T>G (p.Met229Arg), c.686T>C (p.Met229Thr), c.687G>A (p.Met229Ile), c.687G>C (p.Met229Ile), c.687G>T (p.Met229Ile)], in the same codon have been reported in patients with congenital myopathies (PMIDs: 12921789, 19562689, VCEP internal contributor], of which at least two has met the criteria to be classified as pathogenic by the ClinGen Congenital Myopathies VCEP (PM5_Strong). This variant has been reported in a proband with features of congenital myopathy (PS4 not met; Labcorp Genetics, ClinVar Accession: SCV000954285.6). In summary, the variant meets criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy. ACMG/AMP criteria met, as specified by the ClinGen Congenital Myopathies VCEP: PM5_Strong, PM2_P, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0
PP2			The Z-score in gnomAD v2.1.1 is 4.53 which is above the threshold for PP2.

Not Met criteria codes

BP4			The REVEL score is 0.617 which meets neither PP3/BP4.
BP1			The Z-score in gnomAD v2.1.1 is 4.53 which is above the threshold for PP2.
PP3			The REVEL score is 0.617 which meets neither PP3/BP4.

Curation History

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