

Variant: *NM_001100.4(ACTA1):c.685A>G (p.Met229Val)*

Version: 1.0

CA246018 [↗](#)

197716 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e8dcc3d8-e1f4-4926-9e27-80bebb190bd5

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HGVS expressions

NM_001100.4:c.685A>G

NM_001100.4(ACTA1):c.685A>G (p.Met229Val)

NC_000001.11:g.229432117T>C

CM000663.2:g.229432117T>C

NC_000001.10:g.229567864T>C

CM000663.1:g.229567864T>C

NC_000001.9:g.227634487T>C

NG_006672.1:g.6980A>G

ENST00000366683.4:c.685A>G

ENST00000684723.1:c.550A>G

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

ENST00000366684.7:c.685A>G

NM_001100.3:c.685A>G

Pathogenic

Met criteria codes 7

PS2

PP2

PP3

PP4

PM5

PS4_Moderate

PM2_Supporting

Not Met criteria codes 4

BP4

BP1

BA1

BS1

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.685A>G (p.Met229Val) variant in ACTA1 is a missense variant predicted to cause a substitution of methionine by valine at amino acid 229 (p.Met229Val). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). 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 dominant disease (PP2). The computational predictor REVEL gives a score of 0.854, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3). Six different missense variants,

[c.685A>T (p.Met229Leu), 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 one has met the criteria to be classified as pathogenic by the ClinGen Congenital Myopathies VCEP (PM5). This variant has been observed in the heterozygous state in 4 individuals including a de novo occurrence in twins with clinical and histological features compatible with ACTA1-related myopathy including presence of numerous nemaline bodies (PS2, PS4_Moderate, PP4; PMIDs: 19562689, 15236405, 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: PS2, PS4_Moderate, PM5, PM2_Supporting, PP2, PP3, PP4 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0).

Met criteria codes

PS2		✓	This variant has been reported as de novo occurrence in at least one individual (PMIDs: 19562689, 15236405, 12921789).
PP2		✓	ACTA1 is a gene that is constrained for missense variation. The Z-score on gnomAD v4.1.0 is 6.63 meeting PP2.
PP3		✓	The REVEL score is 0.854, which is above the threshold of 0.7 to apply PP3.
PP4		✓	One individual with this variant was reported with pathological findings of type I fiber predominance and numerous nemaline bodies which meets PP4.
PM5		✓	Six different missense variants, [c.685A>T (p.Met229Leu), 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 one has met the criteria to be classified as pathogenic by the ClinGen Congenital Myopathies VCEP.
PS4_Moderate		✓	This variant has been observed in the heterozygous state in four individuals with features of nemaline myopathy (PS4_Moderate; PMIDs: 19562689, 15236405, 12921789).
PM2_Supporting		✓	This variant is absent on gnomAD v4.1, meeting PM2_Supporting.

Not Met criteria codes

BP4		✗	The REVEL score is 0.854, which is above the threshold of 0.7 to apply PP3.
BP1		✗	Missense variant in a gene for which primarily truncating variants are known to cause disease.
BA1		✗	This variant is absent on gnomAD v4.1, meeting PM2_Supporting.
BS1		✗	This variant is absent on gnomAD v4.1, meeting PM2_Supporting.

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