

Variant: NM_001100.4:c.687G>A

Version: 1.0

CA345147057 [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 330bea44-2e46-43fd-b1da-2c8f0f3e0275

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HGVS expressions

NM_001100.4:c.687G>A

NC_000001.11:g.229432115C>T

CM000663.2:g.229432115C>T

NC_000001.10:g.229567862C>T

CM000663.1:g.229567862C>T

NC_000001.9:g.227634485C>T

NG_006672.1:g.6982G>A

ENST00000366683.4:c.687G>A

ENST00000684723.1:c.552G>A

ENST00000366683.3:c.480-253G>A

ENST00000366684.7:c.687G>A

NM_001100.3:c.687G>A

Pathogenic

Met criteria codes **6**

PS2_Moderate

PM5_Strong

PP2

PP3

PM2_Supporting

PS4_Supporting

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*

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

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

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001100.4(ACTA1):c.687G>A variant in ACTA1 is a missense variant predicted to cause substitution of methionine by isoleucine at amino acid 229 (p.Met229Ile, also known as p.Met227Thr). This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.842, 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). Different missense variants (c.686T>C (p.Met229Thr), c.685A>T (p.Met229Leu) and c.685A>G (p.Met229Val)) in the same codon have been classified as

pathogenic/ likely pathogenic for alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5_Strong; SCV007612356.1, SCV007612355.1, SCV007612357.1). This variant has been reported in two probands with clinical features of congenital myopathies, of which one was a de novo case with confirmed parental relationship (PS4_Supporting, PS2_Moderate; PMID: 38544359, 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: PM2_Supporting, PP3, PP2, PM5_Strong, PS4_Supporting, PS2_Moderate (ClinGen Congenital Myopathies VCEP specifications version 2.0)

Met criteria codes

PS2_Moderate			This variant has been identified as a de novo occurrence with confirmed parental relationships in at least one individual with clinical features of congenital myopathy (PS2_Moderate; PMID: 38544359).
PM5_Strong			Different missense variants (c.686T>C (p.Met229Thr), c.685A>T (p.Met229Leu) and c.685A>G (p.Met229Val)) in the same codon have been classified as pathogenic/ likely pathogenic for alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5_Strong; SCV007612356.1, SCV007612355.1, SCV007612357.1).
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 0.842, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).
PM2_Supporting			This variant is absent from gnomAD v4.1.1 (PM2_Supporting).
PS4_Supporting			This variant has been reported in two probands with clinical features of congenital myopathies (PS4_Supporting; PMID: 12921789, 38544359).

Curation History



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