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Variant: NM_001100.4:c.686T>G

Version: 1.0

CA345147066

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2d89e149-6f8f-4828-9aaa-025bc0c6e0f3
Approved on: Mon, 14 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_001100.4:c.686T>G
NC_000001.11:g.229432116A>C
CM000663.2:g.229432116A>C
NC_000001.10:g.229567863A>C
CM000663.1:g.229567863A>C
NC_000001.9:g.227634486A>C
NG_006672.1:g.6981T>G
ENST00000366683.4:c.686T>G
ENST00000684723.1:c.551T>G
ENST00000366683.3:c.480-254T>G
ENST00000366684.7:c.686T>G
NM_001100.3:c.686T>G

Likely Pathogenic

Met criteria codes 5

PM5_Strong PM6_Supporting PM2_Supporting PP2 PP3

Not Met criteria codes 1

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*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001100.4(ACTA1):c.686T>G variant in ACTA1 is a missense variant predicted to cause substitution of methionine by arginine at amino acid 229 (p.Met229Arg). This variant is absent from gnomAD v.4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.94, which is above the VCEP 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 missense variants, [c.686T>C (p.Met229Thr), c.685A>T (p.Met229Leu), and c.685A>G (p.Met229Val); SCV007612356.1, SCV007612355.1, SCV007612357.1, respectively] in the same

codon have been classified as pathogenic or likely pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5_Strong). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with features of ACTA1-related myopathy including proximal myopathy and delayed onset of walking (PM6_Supporting; VCEP internal contributor). In summary, this variant meets the criteria to be classified as likely 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, PM6_Supporting (ClinGen Congenital Myopathies VCEP Specifications Version 2.0).

Met criteria codes

PM5_Strong	✔	Three missense variants, [c.686T>C (p.Met229Thr), c.685A>T (p.Met229Leu), and c.685A>G (p.Met229Val); SCV007612356.1, SCV007612355.1, SCV007612357.1, respectively] in the same codon have been classified as pathogenic/likely pathogenic/pathogenic for autosomal dominant alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5_Strong).
PM6_Supporting	✔	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with features of RYR1-related myopathy (PM6_Supporting, 0.5 points; Synnovis internal data).
PM2_Supporting	✔	This variant is absent from gnomAD (PM2_Supporting). Coverage of the gene in this region is adequate.
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 missense Z-score in gnomAD v4.1.1 is 6.63.
PP3	✔	The computational predictor REVEL gives a score of 0.94, which is above the VCEP threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).

Not Met criteria codes

PS4	✖	There were not enough affected individuals with the variant to apply PS4 at any level.

Curation History

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