

Variant: *NM_001100.4(ACTA1):c.1054T>C (p.Ser352Pro)*

Version: 1.0

CA345144596 [↗](#)

464113 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e57fd35d-43ff-47b8-a169-a06e148fa7c3

Approved on: 2024/8/27

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HGVS expressions

NM_001100.4(ACTA1):c.1054T>C (p.Ser352Pro)

NM_001100.4:c.1054T>C

NC_000001.11:g.229431579A>G

CM000663.2:g.229431579A>G

NC_000001.10:g.229567326A>G

CM000663.1:g.229567326A>G

NC_000001.9:g.227633949A>G

NG_006672.1:g.7518T>C

ENST00000366683.4:c.991-15T>C

ENST00000684723.1:c.919T>C

ENST00000366683.3:c.685T>C

ENST00000366684.7:c.1054T>C

NM_001100.3:c.1054T>C

Likely Pathogenic

Met criteria codes **5**

PM6

PS4_Supporting

PM2_Supporting

PP2

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_001100.3:c.1054T>C in ACTA1 is a missense variant predicted to cause substitution of serine by proline at amino acid 352 (p.Ser352Pro). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.942, which is above the threshold necessary to apply 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). There is no published data on this variant, however Invitae has reported the variant in three

unrelated probands, two of which presented with hypotonia (PS4_Supporting; SCV000638354.5). In addition, one of these probands had a de novo occurrence of the variant with parental relationships unconfirmed (PM6). 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 congenital myopathies VCEP: PM2_Supporting, PP2, PP3, PS4_Supporting, PM6 (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PM6			The variant was determined to be de novo through family studies, however maternity/paternity was not confirmed (Invitae internal data).
PS4_Supporting			There is no published data on this variant, however Invitae has reported the variant in three unrelated probands, two of which presented with hypotonia (PS4_Supporting; SCV000638354.5).
PM2_Supporting			Not present in gnomAD 4.1.0, but has adequate genome/exome coverage
PP2			ACTA1, in which the variant was identified, is defined by the ClinGen CM 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). gnomAD 4.1.0 Z score = 6.09
PP3			The REVEL computational prediction analysis tool produced a score of 0.942, which is above the threshold 0.7 necessary to apply PP3

Curation History



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