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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
Published on: 2024/12/16

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 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 2.0.0*
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).
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
PM2_Supporting	✔	Not present in gnomAD 4.1.0, but has adequate genome/exome coverage
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).

Curation History

Showing 1 to 1 of 1 rows

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