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Variant: NM_001100.4(ACTA1):c.443G>T (p.Gly148Val)

Version: 1.0

CA345149129

2582809 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 82543f83-0695-42b5-9731-c6117f232543
Approved on: 2025/3/10
Published on: 2025/4/1

HGVS expressions

NM_001100.4:c.443G>T
NM_001100.4(ACTA1):c.443G>T (p.Gly148Val)
NC_000001.11:g.229432567C>A
CM000663.2:g.229432567C>A
NC_000001.10:g.229568314C>A
CM000663.1:g.229568314C>A
NC_000001.9:g.227634937C>A
NG_006672.1:g.6530G>T
ENST00000366683.4:c.443G>T
ENST00000684723.1:c.308G>T
ENST00000366683.3:c.443G>T
ENST00000366684.7:c.443G>T
NM_001100.3:c.443G>T

Likely Pathogenic

Met criteria codes 5

PM5 PM6 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 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Congenital Myopathies VCEP

The variant NM_001100.4:c.442G>T in ACTA1 is a missense variant predicted to cause substitution of glycine by valine at amino acid 148 (p.Gly148Val). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.963, 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). Two different missense variants, p.Gly148Ser and p.Gly148Arg (Variation IDs: 1364817 and 280732),

in the same codon have been classified as likely pathogenic for alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5). This variant has been reported in 1 proband with alpha-actinopathy, and had a de novo occurrence of the variant with parental relationships unconfirmed (PM6; PMID: 32668698). In summary, this variant meets the criteria to be classified as likely pathogenic for AD alpha-actinopathy. ACMG/AMP criteria met, as specified by the Congenital Myopathies VCEP (Specification Version 2.0.0): PM2_Supporting, PP3, PP2, PM5, PM6 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0; 3/10/2025).

Met criteria codes

PM5	✔	Two different missense variants, c.442G>A and c.442G>C (Variation IDs: 1364817 and 280732), in the same codon have been classified as likely pathogenic for alpha-actinopathy by the ClinGen Congenital Myopathies VCEP
PM6	✔	One proband had a de novo occurrence of the variant with parental relationships unconfirmed (PMID: 32668698)
PM2_Supporting	✔	The variant is absent from GnomAD v4.1.0
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
PP3	✔	The REVEL computational prediction analysis tool produced a score of 0.963, which is above the threshold necessary to apply PP3

Not Met criteria codes

PS4	✖	One proband with the variant has been reported (PMID: 32668698)

Curation History

Showing 1 to 1 of 1 rows

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