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Variant: NM_001100.4(ACTA1):c.442G>C (p.Gly148Arg)

Version: 1.0

CA10602749

280732 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: bf278676-8839-418d-8172-5dfe7e2b7758
Approved on: 2025/3/10
Published on: 2025/4/1

HGVS expressions

NM_001100.4(ACTA1):c.442G>C (p.Gly148Arg)
NM_001100.4:c.442G>C
NC_000001.11:g.229432568C>G
CM000663.2:g.229432568C>G
NC_000001.10:g.229568315C>G
CM000663.1:g.229568315C>G
NC_000001.9:g.227634938C>G
NG_006672.1:g.6529G>C
ENST00000366683.4:c.442G>C
ENST00000684723.1:c.307G>C
ENST00000366683.3:c.442G>C
ENST00000366684.7:c.442G>C
NM_001100.3:c.442G>C

Likely Pathogenic

Met criteria codes 5

PS2 PP2 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 18

BP5 BP7 BP3 BP1 BP2 PS3 PP1 PP4 PM1 PM3 PM4 PM6 BA1 PVS1 BS1 BS4 BS3 BS2

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>C in ACTA1 is a missense variant predicted to cause substitution of glycine by arginine at amino acid 148 (p.Gly148Arg). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.979, 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.Gly148Val (Variation IDs: 1364817 and 2582809), in the same codon have been classified as likely pathogenic for alpha-actinopathy by the ClinGen Congenital Myopathies VCEP (PM5 applied to p.Gly148Val). This variant has been reported in 2 probands with alpha-actinopathy, and one of these probands had a de novo occurrence of the variant with parental relationships confirmed (PS4_Supporting, PS2; PMID: 33820833. SCV000330673.6). 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, PS4_Supporting, PS2 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0; 3/10/2025).

Met criteria codes

PS2	✔	GeneDx reported this variant as de novo via trio testing and sequencing data was suggestive of mosaicism as the variant allele was underrepresented.
PP2	✔	Although the variant is not documented in the literature, other variants resulting in different amino acid changes in the same codon have been described as autosomal dominant as are 90% of ACTA1 variants so this variant is assumed to potentially be autosomal dominant and thus be constrained for missense variants.
PP3	✔	The REVEL computational prediction analysis tool produced a score of 0.935, which is above the threshold necessary to apply PP3
PM2_Supporting	✔	Variant is absent from controls
PS4_Supporting	✔	This variant has been reported in 2 probands with alpha-actinopathy (PMID: 33820833, GeneDx internal data)

Not Met criteria codes

BP5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	Not applicable for missense variant
BP3	✖	Not applicable for missense variant
BP1	✖	Missense variants are a known mechanism of disease
BP2	✖	This is most likely an autosomal dominant variant but no patients in the literature have been observed.
PS3	✖	No functional data
PP1	✖	Segregation data not available
PP4	✖	Probands either did not have muscle biopsies performed or did not show characteristic pathology.

PM1		✖	ACTA1 is not applicable for PM1
PM3		✖	This is most likely an autosomal dominant variant but no patients in the literature have been observed.
PM4	ℹ	✖	Not applicable for missense variant
PM6	ℹ	✖	Maternity and paternity confirmed via trio analysis
BA1	ℹ	✖	Variant is absent from controls
PVS1		✖	Not applicable for missense variant
BS1	ℹ	✖	Variant is absent from controls
BS4	ℹ	✖	Segregation data not available
BS3		✖	No functional data
BS2	ℹ	✖	No available controls had the variant

Curation History

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