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# *Variant: NM_001100.4(ACTA1):c.442G>A (p.Gly148Ser)*

Version: 1.0

*CA221485*

*93549 (ClinVar)*

**Gene**: ACTA1 (HGNC:58)
**Condition**: alpha-actinopathy (MONDO:0100084)
**Inheritance Mode**: Autosomal dominant inheritance
**UUID:** a695743f-28f5-4e59-ad87-db52db959e09
**Approved on**: 2025/3/10
**Published on**: 2025/4/1

## *HGVS expressions*

**NM_001100.4(ACTA1):c.442G>A (p.Gly148Ser)**
**NM_001100.4:c.442G>A**
NC_000001.11:g.229432568C>T
CM000663.2:g.229432568C>T
NC_000001.10:g.229568315C>T
CM000663.1:g.229568315C>T
NC_000001.9:g.227634938C>T
NG_006672.1:g.6529G>A
ENST00000366683.4:c.442G>A
ENST00000684723.1:c.307G>A
ENST00000366683.3:c.442G>A
ENST00000366684.7:c.442G>A
NM_001100.3:c.442G>A

**Likely Pathogenic**

**Met criteria codes** 5

PP2 PP3 PM6 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_001100.4:c.442G>A in ACTA1 is a missense variant predicted to cause substitution of glycine by serine at amino acid 148 (p.Gly148Ser). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.935, 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.Gly148Arg and p.Gly148Val (Variation IDs: 280732 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 3 probands with alpha-actinopathy, and one of these probands had a de novo occurrence of the variant with parental relationships unconfirmed (PS4_Supporting, PM6; PMIDs: 19562689, 32222963. SCV000680134.1). 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, PM6 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0; 3/10/2025).**

**Met criteria codes**

| | | |
|---|---|---|
| **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 0.935, which is above the threshold necessary to apply PP3 |
| **PM6** | ✔ | One proband was reported as a de novo occurrence with unconfirmed parental relationship (Institute of Human Genetics Munich) |
| **PM2_Supporting** | ✔ | Variant absent from GnomAD v4.1.0 |
| **PS4_Supporting** | ✔ | This variant has been reported in 3 probands with alpha-actinopathy, meeting PS4_Supporting (PMID: 32222963, PMID: 19562689, Institute of Human Genetics Munich) |

## Curation History

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