

Variant: *NM_001100.4(ACTA1):c.923A>G (p.Tyr308Cys)*

Version: 1.0

CA10575963 [↗](#)

224672 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 454fe219-c891-4f46-b624-4e5950727a16

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HGVS expressions

NM_001100.4(ACTA1):c.923A>G (p.Tyr308Cys)

NM_001100.4:c.923A>G

NC_000001.11:g.229431788T>C

CM000663.2:g.229431788T>C

NC_000001.10:g.229567535T>C

CM000663.1:g.229567535T>C

NC_000001.9:g.227634158T>C

NG_006672.1:g.7309A>G

ENST00000366683.4:c.923A>G

ENST00000684723.1:c.788A>G

ENST00000366683.3:c.554A>G

ENST00000366684.7:c.923A>G

NM_001100.3:c.923A>G

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP2 PP3 PP4
PP1_Moderate PM2_Supporting

Not Met criteria codes 20

PVS1 BA1 BP5 BP7 BP4
BP3 BP1 BP2 BS1 BS4 BS3
BS2 PM1 PM3 PM5 PM4
PS1 PS2 PS3 PM6

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

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Congenital Myopathies VCEP

The NM_001100.4(ACTA1):c.923A>G (p.Tyr308Cys) variant in ACTA1 is a missense variant predicted to cause a substitution of tyrosine by cysteine at amino acid 308. This variant is absent from gnomAD v4.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.898, which is above the threshold of ≥ 0.7 , evidence that correlates with impact to ACTA1 function (PP3). ACTA1 has a low rate of benign missense variation and pathogenic missense variants are a common mechanism of disease in the autosomal dominant context as

defined by the ClinGen Congenital Myopathies VCEP (PP2). This variant has been identified in the heterozygous state in an individual with a confirmed diagnosis of nemaline myopathy (PP4) (PMID: 32222963). This variant has also been identified in the heterozygous state in individuals with clinical features of myopathy or muscle dystrophy including an affected mother and two children (PP1_Moderate, PS4_Supporting) (PMID: 32222963, VCEP internal contributor). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant ACTA1-related alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PM2_Supporting, PP3, PP2, PP4, PP1_Moderate, and PS4_Supporting (VCEP Specifications Version 2.0).

Met criteria codes

PS4_Supporting			One proband from PMID: 32222963 and a proband from the PathWest diagnostic laboratory in Western Australia (VCEP communication) meet PS4_Supporting criteria.
PP2			PP2 is applicable for autosomal dominant variants in ACTA1 per VCEP specifications
PP3			The REVEL score is 0.891, which is above the 0.7 threshold set by VCEP for damaging predictor
PP4			PMID: 32222963 reported a cohort of 48 patients with confirmed nemaline myopathy. Inclusion criteria included presenting with muscle weakness, delayed motor milestones, or exercise intolerance AND muscle biopsy showing presence of nemaline rods in muscle fibers after light and electron microscopy and lack of other specific pathological findings with other diseases such as immuno-metabolic myopathy, muscular dystrophy, and neurogenetic muscular disorders. An NGS panel of 700 genes identified this variant as HET in P39 who was a 19 year old male with congenital onset, parental testing not available, and no other proband-specific info available. For the presence of nemaline rods, PP4 at supporting level can be applied.
PP1_Moderate			Internal information from the PathWest diagnostic laboratory in Western Australia has two families with the NM_001100.4(ACTA1):c.923A>G (p.Tyr308Cys) variant. In one family there is a single isolated case (proband from PMID: 32153140), in the other there are three affected individuals - a mother and two children. PP1 Moderate for 2 co-segregations for this family.
PM2_Supporting			This variant is absent from gnomAD v4.1.1

Not Met criteria codes

PVS1			Missense variant, criteria not applicable
BA1			Variant is absent from gnomAD v4.1.1
BP5			Not identified in a case with an alternate molecular basis for disease
BP7			Missense variant, criteria not applicable
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP3		✖	Missense variant, criteria not applicable
BP1		✖	BP1 not applicable to ACTA1 per VCEP specifications
BP2		✖	Not observed with another ACTA1 variant
BS1		✖	Variant is absent from gnomAD v4.1.1
BS4		✖	Reported cases have not included familial segregation information
BS3		✖	No functional studies performed for this variant presently
BS2		✖	Variant is absent from gnomAD v4.1.1
PM1		✖	PM1 not applicable per VCEP specifications
PM3		✖	Curating as AD variant, not observed with another ACTA1 variant
PM5		✖	PM5 not applicable: (ACTA1):c.922T>C (p.Tyr308His) VUS in ClinVar, unpublished, absent from gnomAD v4.1.1, damaging REVEL score (PM2_Supporting, PP3) variant currently at VUS
PM4		✖	Missense variant, criteria not applicable
PS1		✖	No previously reported variant resulting in the same amino acid change
PS2		✖	Reported cases have not had familial segregation information
PS3		✖	No functional studies performed for this variant presently
PM6		✖	Reported cases have not had familial segregation information

Curation History [↗](#)

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