The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001100.4(ACTA1):c.617-5C>A

Version: 1.0

CA2499214555

1051987 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 317a5950-15e5-4569-a65a-07f1b3411437
Approved on: 2024-08-27
Published on: 2024-12-16

HGVS expressions

NM_001100.4:c.617-5C>A
NM_001100.4(ACTA1):c.617-5C>A
NC_000001.11:g.229432190G>T
CM000663.2:g.229432190G>T
NC_000001.10:g.229567937G>T
CM000663.1:g.229567937G>T
NC_000001.9:g.227634560G>T
NG_006672.1:g.6907C>A
ENST00000366683.4:c.617-5C>A
ENST00000684723.1:c.482-5C>A
ENST00000366683.3:c.479+217C>A
ENST00000366684.7:c.617-5C>A
NM_001100.3:c.617-5C>A

Uncertain Significance

Met criteria codes 4

PP3 PS4_Supporting PP1_Moderate PM2_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 c.617-5C>A variant in ACTA1 is an intronic variant in the 3’ non-canonical splice site of intron 4. This variant is predicted to create a cryptic splice site, and add one amino acid (Ala) translated from intron 4 to the mature protein, but the exact impact is unknown because no functional studies have been performed. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor SpliceAI gives a score of 1 predicting an acceptor gain, which is above the threshold of 0.5, evidence that correlates with impact to ACTA1 function (PP3). This variant has been reported in two families with myopathy without muscle biopsies and three adults with features of

muscle weakness (PS4_Supporting; PMID: 19562689, Invitae, SCV001556001.2, GeneDx, SCV001986137.1). The variant has been reported to segregate with myopathy in 2 affected family members from 1 family (PP1_Moderate, Invitae, SCV001556001.2). In summary, this variant meets the criteria to be classified as uncertain significance for autosomal dominant alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PS4_Supporting, PP1_Moderate, PM2_Supporting, PP3 (Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PP3	✔	SpilceAI does predict a gain of an acceptor site with a score of 1, which is greater than the CM VCEP 0.5 cutoff to apply PP3.
PS4_Supporting	✔	This variant has been reported in two families with myopathy without muscle biopsies and three adults with features of muscle weakness (PS4_P; PMID: 19562689, Invitae, SCV001556001.2, GeneDx, SCV001986137.1).
PP1_Moderate	✔	The variant has been reported to segregate with myopathy in 2 affected family members from 1 family (PP1_M, Invitae, SCV001556001.2).
PM2_Supporting	✔	The c.617-5C>A variant is absent from gnomAD 4.1.0 with adequate coverage.

Curation History

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