

Variant: NM_001100.4(ACTA1):c.1075A>C (p.Ile359Leu)

Version: 1.0

CA258138 [↗](#)

18284 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b7a20c61-e14f-4740-b35c-e459d2a51945

Approved on: 2024/7/8

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HGVS expressions

NM_001100.4(ACTA1):c.1075A>C (p.Ile359Leu)

NM_001100.4:c.1075A>C

NC_000001.11:g.229431558T>G

CM000663.2:g.229431558T>G

NC_000001.10:g.229567305T>G

CM000663.1:g.229567305T>G

NC_000001.9:g.227633928T>G

NG_006672.1:g.7539A>C

ENST00000366683.4:c.997A>C

ENST00000684723.1:c.940A>C

ENST00000366683.3:c.706A>C

ENST00000366684.7:c.1075A>C

NM_001100.3:c.1075A>C

Pathogenic

Met criteria codes 6

PM2_Supporting

PS3_Moderate

PS2

PP4_Moderate

PP2

PP3

Not Met criteria codes 2

BP4

PS4

Evidence Links 2

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 NM_001100.4:c.1075A>C variant in ACTA1 is a missense variant predicted to cause substitution of isoleucine by leucine at amino acid 359. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.865, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (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). This variant has been identified as a de novo occurrence with confirmed

parental relationships in 1 individual with autosomal dominant alpha-actinopathy (PS2; PMID: 11333380). At least one patient with this variant displayed nemaline bodies and intranuclear rods, which is highly specific for autosomal dominant alpha-actinopathy (PP4_Moderate, PMID: 11333380). Actin localization in patient muscle biopsies showed abnormal localization of actin indicating that this variant impacts protein function (PMID: 11333380). Actin polymerization in expressed α -skeletal-muscle actins (wild-type and mutants) as 35S-labeled proteins by in vitro transcription translation reactions in reticulocyte lysate showed impaired co-polymerization of I357L actin with wild-type rabbit α -skeletal-muscle actin indicating that this variant impacts protein function (PMID:15226407) (PS3_Moderate). In summary, this variant meets the criteria to be classified as pathogenic for autosomal dominant alpha-actinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen Congenital Myopathies VCEP: PS2, PS3_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3. (ClinGen Congenital Myopathies VCEP specifications version 2.0.0; July 8th, 2024)

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0
PS3_Moderate			In vitro functional studies show evidence that this variant impacts protein function (PMIDs: 11333380, 15226407) Actin localization in patient muscle biopsies showed abnormal localization of actin indicating that this variant impacts protein function PubMed:11333380  Actin polymerization in expressed α-skeletal-muscle actins (wild-type and mutants) as 35S-labeled proteins by in vitro transcription translation reactions in reticulocyte lysate showed impaired co-polymerization of I357L actin with wild-type rabbit α-skeletal-muscle actin indicating that this variant impacts protein function PubMed:15226407 
PS2			This variant has been identified as a de novo occurrence with confirmed parental relationships in 1 individual with autosomal dominant alpha-actinopathy (PMID: 11333380).
PP4_Moderate			The patient displayed nemaline bodies and intranuclear rods, which is highly specific for autosomal dominant alpha-actinopathy (PMID: 11333380).
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 computational predictor REVEL gives a score of 0.865, which is above the threshold of 0.7

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.865
PS4			Only one proband with myopathy was reported with this variant.

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