

Variant: NM_001100.4(ACTA1):c.1127G>T (p.Cys376Phe)

Version: 1.0

CA345144073 [↗](#)

801630 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: b2f5e908-7dc7-4115-af99-78db860db1e1

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HGVS expressions

NM_001100.4(ACTA1):c.1127G>T (p.Cys376Phe)

NM_001100.4:c.1127G>T

NC_000001.11:g.229431506C>A

CM000663.2:g.229431506C>A

NC_000001.10:g.229567253C>A

CM000663.1:g.229567253C>A

NC_000001.9:g.227633876C>A

NG_006672.1:g.7591G>T

ENST00000366683.4:c.1049G>T

ENST00000684723.1:c.992G>T

ENST00000366683.3:c.758G>T

ENST00000366684.7:c.1127G>T

NM_001100.3:c.1127G>T

Likely Pathogenic

Met criteria codes 5

PS2 PP2 PP3 PM5

PM2_Supporting

Not Met criteria codes 21

BA1 PS1 PS3 PS4 PP1 PP4

PM6 PM1 PM3 PM4 BS1

BS4 BS3 BS2 PVS1 BP5

BP7 BP4 BP3 BP1 BP2

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.1127G>T in ACTA1 is a missense variant predicted to cause substitution of cysteine by phenylalanine at amino acid 376 (p.Cys376Phe) in exon 7/7. The variant is absent from gnomAD v4.1.1 with adequate coverage (PM2_Supporting). The REVEL computational prediction analysis tool gives a score of 0.955, which is above the threshold necessary to apply PP3. In addition, 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 reported as a de novo observation with confirmed parental relationships in one proband with features associated with congenital myopathy which meets the criteria for PS2 (Invitae, SCV002228646.2). Another missense variant c.1127G>C (p.Cys376Ser) in the same codon is classified as pathogenic for autosomal dominant alpha-actinopathy (PM5, PMIDs:25890230, 19562689). In summary, the variant meets the criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy. ACMG/AMP criteria met, as specified by the ClinGen Congenital Myopathies VCEP: PS2, PM5, PP2, PP3, PM2_Supporting (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PS2			This variant has been identified as a de novo occurrence with confirmed parental relationships in an individual (Invitae, SCV002228646.2).
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. The missense Z-score in gnomAD v4.1.1 is 6.09 which is above the threshold set by the ClinGen Congenital Myopathies VCEP.
PP3			The computational predictor REVEL gives a score of 0.955, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3)
PM5			c.1127G>C(p.Cys376Ser) in the same codon is classified as pathogenic for autosomal dominant alpha-actinopathy
PM2_Supporting			This variant is absent from gnomAD v.4.1.1 with adequate coverage (PM2_Supporting)

Not Met criteria codes

BA1			This variant is absent from gnomAD v.2.1.1
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			This variant has been reported in one proband, an infant with severely flaccidity, lower leg spasticity, hypotonia, pronounced facial weakness, joint contractures, inability to swallow (fed via gastric tube) (Invitae internal data, SCV000934090.3).
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is absent from gnomAD v.2.1.1
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			The computational predictor REVEL gives a score of 0.955
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline











Showing 1 to 1 of 1 rows

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