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.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
Approved on: 2024/8/27
Published on: 2025/1/3

HGVS expressions

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

PP2 PP3 PM5 PS2 PM2_Supporting

Not Met criteria codes 21

PP1 PP4 PM6 PM1 PM3 PM4 BA1 BS2 BS1 BS4 BS3 PS1 PS3 PS4 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

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
PS2	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in an individual (Invitae, SCV002228646.2).
PM2_Supporting	✔	This variant is absent from gnomAD v.4.1.1 with adequate coverage (PM2_Supporting)

Not Met criteria codes

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

BA1	ℹ	✖	This variant is absent from gnomAD v.2.1.1
BS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	ℹ	✖	This variant is absent from gnomAD v.2.1.1
BS4	ℹ	✖	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
PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4	ℹ	✖	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).
PVS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	ℹ	✖	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	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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