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Variant: NM_001100.4:c.1127G>C

Version: 1.0

CA345144077

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: e4571073-5716-435c-8a48-25ed7fb25a0c
Approved on: 2024-08-27
Published on: 2024-12-16

HGVS expressions

NM_001100.4:c.1127G>C
NC_000001.11:g.229431506C>G
CM000663.2:g.229431506C>G
NC_000001.10:g.229567253C>G
CM000663.1:g.229567253C>G
NC_000001.9:g.227633876C>G
NG_006672.1:g.7591G>C
ENST00000366683.4:c.1049G>C
ENST00000684723.1:c.992G>C
ENST00000366683.3:c.758G>C
ENST00000366684.7:c.1127G>C
NM_001100.3:c.1127G>C

Pathogenic

Met criteria codes 6

PS2 PP2 PP3 PP4_Moderate PM2_Supporting PS4_Supporting

Not Met criteria codes 16

PS1 PS3 BA1 PVS1 PM1 PM3 PM5 PM4 BS1 BS3 BS2 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>C in ACTA1 is a missense variant predicted to cause substitution of cysteine by serine at amino acid 376 (p.Cys376Ser) in exon 7/7. The variant is absent from gnomAD v2.1.1 with adequate coverage (PM2_Supporting). The REVEL computational prediction analysis tool gives a score of 0.946, 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). The Z-score in gnomAD v2.1.1 is 4.53 which is above the threshold necessary to apply PP2. This variant has been reported in two probands with congenital nemaline myopathy

(PS4_Supporting, PP4_Moderate PMID:25890230,19562689), and as a de novo observation with confirmed parental relationships in one of the probands (PS2, PMID:25890230). In summary, the variant meets the criteria to be classified as Pathogenic for autosomal dominant alpha-actinopathy. ACMG/AMP criteria met, as specified by the ClinGen Congenital Myopathies VCEP: PS2, PP4_Moderate, PS4_Supporting, PP2, PP3, PM2_Supporting (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PS2	✔	One proband was identified as de novo with confirmed parental relationships (PMID: 25890230)
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 Z-score in gnomAD v4.1.0 is 6.09 which is above the threshold for PP2
PP3	✔	The REVEL score is 0.946, which is above the threshold of 0.7 to apply PP3
PP4_Moderate	✔	This variant has been reported in two probands with congenital nemaline myopathy (PMID:25890230,19562689). One of these probands had a skeletal muscle biopsy that displayed features specific for nemaline myopathy.
PM2_Supporting	✔	This variant is absent from gnomAD v.4.1.0 with adequate coverage
PS4_Supporting	✔	There are two probands with nemaline myopthy reported in two publications (PMID:25890230, 19562689)

Not Met criteria codes

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
BA1	✖	This variant is absent from gnomAD v.2.1.1 with adequate coverage
PVS1	✖	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
PM5	✖	PM5 applied to c.1127G>T(p.Cys376Phe) curation

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 with adequate coverage
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
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	The REVEL score is 0.946
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

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001100.4:c.1127G>C	Pathogenic	Alpha-Actinopathy	2024-12-16	1.0	ClinGen Congenital Myopathies Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACTA1 Version 2.0.0	ACTA1

Showing 1 to 1 of 1 rows