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Variant: NM_001100.4(ACTA1):c.124C>T (p.His42Tyr)

Version: 1.0

CA345151235

1452968 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: ac6e8233-e5c6-4ff0-b854-961d3d2c5944
Approved on: 2024/8/27
Published on: 2024/12/12

HGVS expressions

NM_001100.4:c.124C>T
NM_001100.4(ACTA1):c.124C>T (p.His42Tyr)
NC_000001.11:g.229432992G>A
CM000663.2:g.229432992G>A
NC_000001.10:g.229568739G>A
CM000663.1:g.229568739G>A
NC_000001.9:g.227635362G>A
NG_006672.1:g.6105C>T
ENST00000366683.4:c.124C>T
ENST00000684723.1:c.-6-112C>T
ENST00000366683.3:c.124C>T
ENST00000366684.7:c.124C>T
NM_001100.3:c.124C>T

Pathogenic

Met criteria codes 7

PM2_Supporting PP4_Moderate PS4_Moderate PS2 PS3 PP2 PP3

Not Met criteria codes 4

BS1 BS3 BP4 BA1

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 NM_001100.4:c.124C>T variant in ACTA1 is a missense variant predicted to cause substitution of histidine by tyrosine at amino acid 42 (legacy nomenclature: p.His40Tyr). This variant is absent from gnomAD v4.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.72, 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). In vitro studies demonstrated changes in actin

localization and motility (PMID:15226407, 17227580, 27112274). In vivo studies in a mouse model demonstrated impaired function of ACTA1 and limited intrinsic force-generating capacity and maximal tetanic force (PMID:23613869, 23656990)(PS3). This variant has been reported in 4 probands/families with intranuclear rod and/or nemaline myopathies (PS4_Moderate; PMID:10508519, 12921789, 19562689). This variant has occured de novo with confirmed parental relationships in 1 individual and was reported to occur de novo with unconfirmed parental relationships in 1 individual with severe atypical nemaline myopathy with intranuclear nemaline bodies (PS2, PP4_Moderate; PMID:10508519, 19562689). 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, PS4_Moderate, PP4_Moderate, PM2_Supporting, PP2, PP3 (Congenital Myopathies VCEP specifications version 2; 08/27/2024.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1 (PM2_Supporting).
PP4_Moderate	✔	This variant has occured de novo with confirmed parental relationships in 1 individual and was reported to occur de novo with unconfirmed parental relationships in 1 individual with severe atypical nemaline myopathy with intranuclear nemaline bodies (PS2, PP4_Moderate; PMID:10508519, 19562689).
PS4_Moderate	✔	This variant has been reported in 4 probands/families with intranuclear rod and/or nemaline myopathies (PS4_Moderate; PMID:10508519, 12921789, 19562689).
PS2	✔	This variant has occured de novo with confirmed parental relationships in 1 individual and was reported to occur de novo with unconfirmed parental relationships in 1 individual with severe atypical nemaline myopathy with intranuclear nemaline bodies (PS2; PMID:10508519, 19562689).
PS3	✔	In vitro studies demonstrated changes in actin localization and motility (PMID:15226407, 17227580, 27112274). In vivo studies in a mouse model demonstrated impaired function of ACTA1 and limited intrinsic force-generating capacity and maximal tetanic force (PMID:23613869, 23656990)(PS3).
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 (PP2).
PP3	✔	The computational predictor REVEL gives a score of 0.72, which is above the threshold of 0.7, evidence that correlates with impact to ACTA1 function (PP3).

Not Met criteria codes

BS1	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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