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Variant: NM_001100.4(ACTA1):c.414C>G (p.Ile138Met)

Version: 1.0

CA258142

18286 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: e8c39b71-4332-4f96-9fcd-9a2038093ac4
Approved on: 2024/8/27
Published on: 2024/12/16

HGVS expressions

NM_001100.4(ACTA1):c.414C>G (p.Ile138Met)
NM_001100.4:c.414C>G
NC_000001.11:g.229432596G>C
CM000663.2:g.229432596G>C
NC_000001.10:g.229568343G>C
CM000663.1:g.229568343G>C
NC_000001.9:g.227634966G>C
NG_006672.1:g.6501C>G
ENST00000366683.4:c.414C>G
ENST00000684723.1:c.279C>G
ENST00000366683.3:c.414C>G
ENST00000366684.7:c.414C>G
NM_001100.3:c.414C>G

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP2 PP3 PP4_Moderate PS3

Not Met criteria codes 1

PS4

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.414C>G in ACTA1 is a missense variant predicted to cause substitution of isoleucine by methionine at amino acid 138 (p.Ile138Met). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.799, which is above the threshold necessary to apply 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 addition, functional studies have demonstrated that this variant severely reduces

co-polymerization compared to wild-type actin, and reduces flight ability in Drosophila (PS3; PMIDs: 15226407, 23294764). This variant has been reported in one proband, who has nemaline rods and thin filament accumulation present on muscle biopsy (PP4_Moderate; PMIDs: 11333380, 10838259). In summary, the variant meets criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy. ACMG/AMP criteria met, as specified by the congenital myopathies VCEP: PS3, PP4_Moderate, PM2_Supporting, PP2, PP3, (ClinGen Congenital Myopathies VCEP specifications version 2; 08/27/2024).

Met criteria codes

PM2_Supporting	✔	The variant is absent from gnomAD v.4.1.0.
PP2	✔	ACTA1, in which the variant was identified, is defined by the ClinGen CM VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease. gnomAD 4.1.0 Z score = 6.09
PP3	✔	The REVEL computational predictor produced a score of 0.799, which is above the threshold of 0.7 set by the CM VCEP to apply PP3.
PP4_Moderate	✔	This variant has been reported in one proband, who has nemaline rods and thin filament accumulation present on muscle biopsy (PP4_Moderate; PMIDs: 11333380, 10838259).
PS3	✔	Functional studies have demonstrated that this variant severely reduces co-polymerization compared to wild-type actin, and that it also reduces flight ability of Drosophila and affects F-actin organization in myofibrils and Z-disc organization.

Not Met criteria codes

PS4	✖	This variant has been reported in one proband, who has nemaline rods and thin filament accumulation present on muscle biopsy (PP4_Moderate; PMIDs: 11333380, 10838259).

Curation History

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