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Variant: NM_001100.4(ACTA1):c.686T>C (p.Met229Thr)

Version: 1.0

CA345147061

2635623 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: a4cb3486-db59-4166-810b-1b8f655301da
Approved on: 2026/6/8
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HGVS expressions

NM_001100.4(ACTA1):c.686T>C (p.Met229Thr)
NM_001100.4:c.686T>C
NC_000001.11:g.229432116A>G
CM000663.2:g.229432116A>G
NC_000001.10:g.229567863A>G
CM000663.1:g.229567863A>G
NC_000001.9:g.227634486A>G
NG_006672.1:g.6981T>C
ENST00000366683.4:c.686T>C
ENST00000684723.1:c.551T>C
ENST00000366683.3:c.480-254T>C
ENST00000366684.7:c.686T>C
NM_001100.3:c.686T>C

Pathogenic

Met criteria codes 5

PS2 PP2 PP3 PS4_Supporting PM2_Supporting

Not Met criteria codes 5

BA1 PM5 BS1 BP4 BP1

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.686T>C in ACTA1 is a missense variant predicted to cause substitution of methionine by threonine at amino acid 229 (p.Met229Thr). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The REVEL computational prediction analysis tool produced a score of 0.934, which is above the threshold predicting a damaging impact on ACTA1 function. 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). Six different missense variants, [c.685A>G (p.Met229Val),

c.686T>G (p.Met229Arg), c.685A>T (p.Met229Leu), c.687G>A (p.Met229Ile), c.687G>C (p.Met229Ile), c.687G>T (p.Met229Ile)], in the same codon have been reported in patients with congenital myopathies (PMIDs: 12921789, 19562689, VCEP internal contributor]. This variant has been reported as de novo occurrences in at least three probands with features of nemaline myopathy, of which one was de novo with confirmed parentage (PS2, PS4_Supporting; PMIDs: 12921789, 19562689, 35810298, 38982518, 40225930; Institut de Génétique et Biologie Moléculaire et Cellulaire, ClinVar Accession: SCV005038471.2). At least one patient with this variant displayed characteristic muscle biopsy with fiber size variability, intranuclear rods, cytoplasmic bodies, and other features, which is highly compatible with alpha-actinopathy (PP4_Moderate, PMIDs:35810298, 38982518). In summary, the variant meets 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_M, PS4_P, PM2_P, PP2, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0).

Met criteria codes

PS2	✔	Three probands have been reported as de novo occurrences with features of nemaline myopathy, of which one was de novo with confirmed parentage (PS2, PMIDs: 12921789, 19562689, 35810298, 38982518, 40225930; Institut de Génétique et Biologie Moléculaire et Cellulaire, ClinVar Accession: SCV005038471.2).
PP2	✔	The Z-score in gnomAD v2.1.1 is 4.53 which is above the threshold for PP2.
PP3	✔	The REVEL score is 0.934 which is above the threshold to apply PP3.
PS4_Supporting	✔	This variant has been reported in at least three probands with features of nemaline myopathy (PS4_Supporting; PMIDs: 12921789, 19562689, 35810298, 38982518, 40225930; Institut de Génétique et Biologie Moléculaire et Cellulaire, ClinVar Accession: SCV005038471.2).
PM2_Supporting	✔	The variant is absent from gnomAD v4.1.0

Not Met criteria codes

BA1	✖	The variant is absent from gnomAD v4.1.0
PM5	✖	Six different variants in the same residue have been identified in patients with congenital myopathy, however PM5 was applied to the other variants.
BS1	✖	The variant is absent from gnomAD v4.1.0
BP4	✖	The REVEL score is 0.934 which is above the threshold to apply PP3.
BP1	✖	The Z-score in gnomAD v2.1.1 is 4.53 which is above the threshold for PP2.

Curation History

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