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Variant: NM_001100.4(ACTA1):c.175G>A (p.Glu59Lys)

Version: 1.2

CA345150851

2582036 (ClinVar)

Gene: ACTA1 (HGNC:58)
Condition: alpha-actinopathy (MONDO:0100084)
Inheritance Mode: Autosomal dominant inheritance
UUID: 2aee884c-3b70-4401-b302-863a80a893a3
Approved on: 2024/9/9
Published on: 2025/4/1

HGVS expressions

NM_001100.4:c.175G>A
NM_001100.4(ACTA1):c.175G>A (p.Glu59Lys)
NC_000001.11:g.229432835C>T
CM000663.2:g.229432835C>T
NC_000001.10:g.229568582C>T
CM000663.1:g.229568582C>T
NC_000001.9:g.227635205C>T
NG_006672.1:g.6262G>A
ENST00000366683.4:c.175G>A
ENST00000684723.1:c.40G>A
ENST00000366683.3:c.175G>A
ENST00000366684.7:c.175G>A
NM_001100.3:c.175G>A

Likely Pathogenic

Met criteria codes 5

PM6 PP2 PP3 PM2_Supporting PS4_Supporting

Not Met criteria codes 4

BA1 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 NM_001100.4:c.175G>A variant in ACTA1 is a missense variant predicted to cause substitution of glutamate by lysine at amino acid 59 (p.Glu59Lys). The variant is absent from gnomAD v4.1.0 meeting PM2_Supporting. The REVEL computational prediction analysis tool gives a score of 0.855, 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. The Z-score in gnomAD v4.1 is 4.53 (PP2). This variant has been reported in at least three probands, of

which one was a de novo occurrence with unconfirmed parental relationships (PS4_Supporting, PM6; GeneDx, Harry Perkins Institute Of Medical Research, LabCorp internal data, ClinVar: SCV004040176.2, SCV004041839.1). 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: PM6, PS4_Supporting, PM2_Supporting, PP2, PP3 (ClinGen Congenital Myopathies VCEP specifications version 2.0.0; 9/9/2024).

Met criteria codes

PM6	✔	The variant was reported de novo with unconfirmed parental relationships in a proband (Harry Perkins Institute Of Medical Research, University Of Western Australia)
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 v2.1.1 is 4.53
PP3	✔	The REVEL score was 0.855, which is above the threshold of 0.7 to apply PP3
PM2_Supporting	✔	This variant was absent from gnomAD v4 meeting PM2_Supporting
PS4_Supporting	✔	This variant was reported in three individuals with muscular weakness and dilated cardiomyopathy meeting PS4_Supporting (GeneDx, LabCorp, Harry Perkins Institute of Medical Research)

Not Met criteria codes

BA1	✖	This variant was absent from gnomAD v4 meeting PM2_Supporting
BS1	✖	This variant was absent from gnomAD v4 meeting PM2_Supporting
BP4	✖	The REVEL score was 0.855, which is above the threshold of 0.7 to apply PP3
BP1	✖	Both missense and truncating variants in ACTA1 are disease-causing.

Curation History

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