

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

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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

PS4_Supporting

PM2_Supporting

PP2

PP3

Not Met criteria codes **4**

BS1

BP4

BP1

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.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)
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)
PM2_Supporting			This variant was absent from gnomAD v4 meeting PM2_Supporting
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

Not Met criteria codes

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.
BA1			This variant was absent from gnomAD v4 meeting PM2_Supporting

Curation History 

