

Variant: *NM_001100.4(ACTA1):c.37G>A (p.Asp13Asn)*

Version: 1.0

CA345151718 [↗](#)

642798 (ClinVar) [↗](#)

Gene: ACTA1 ([HGNC:58](#))

Condition: alpha-actinopathy ([MONDO:0100084](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 81bf4e47-2384-4391-8fc9-1fd751d9fa35

Approved on: 2024/12/9

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HGVS expressions

NM_001100.4:c.37G>A

NM_001100.4(ACTA1):c.37G>A (p.Asp13Asn)

NC_000001.11:g.229433079C>T

CM000663.2:g.229433079C>T

NC_000001.10:g.229568826C>T

CM000663.1:g.229568826C>T

NC_000001.9:g.227635449C>T

NG_006672.1:g.6018G>A

ENST00000366683.4:c.37G>A

ENST00000684723.1:c.-6-199G>A

ENST00000366683.3:c.37G>A

ENST00000366684.7:c.37G>A

NM_001100.3:c.37G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS2 PP2 PP3

Not Met criteria codes 22

BS2 BS1 BS4 BS3 PVS1
BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS3 PS4 BA1 PP1 PP4
PM6 PM1 PM3 PM5 PM4

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.37G>A (p.Asp13Asn) variant in ACTA1 is a missense variant predicted to cause a substitution of aspartic acid by asparagine at amino acid 13. ACTA1 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). The computational predictor REVEL gives a score of 0.763, which is above the threshold for predicting a damaging effect on ACTA1 variants (PP3). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The variant has been identified as de novo by trio analysis in one proband with clinical features of

congenital myopathy (ARUP Laboratories; SCV001157803.1) (PS2). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal dominant alpha-actinopathy based on the ACMG/AMP criteria applied as specified by the ClinGen Congenital Myopathy VCEP: PP2, PP3, PM2_Supporting, PS2; ClinGen Congenital Myopathies VCEP Specifications 2.0.0; 12/9/2024			
Met criteria codes			
PM2_Supporting			Absent from gnomAD, ExAC, and 1000 Genomes
PS2			According to ARUP, their patient with the variant was found to have the variant de novo by trio analysis
PP2			The c.37G>A (p.Asp13Asn) variant is a missense variant in ACTA1 which is constrained for missense variants.
PP3			Multiple lines of computational evidence support a deleterious effect with on the gene or gene product including a REVEL score >0.7 as specified in VCEP's PP3 criteria
Not Met criteria codes			
BS2			Absent from population databases and dominant ACTA1 mutations are not fully penetrant per PMID: 19562689
BS1			Absent from gnomAD, ExAC, and 1000 Genomes
BS4			Segregation data not available
BS3			No functional studies of variant available.
PVS1			Missense variant not affecting canonical splice sites
BP5			In PMID: 19562689 patient with variant was diagnosed with NMR however there could be overlap with other congenital myopathy phenotypes, GeneDx reported that the proband was negative for a NEB exon 55 deletion. ARUP reported their proband had distal arthrogryposis, central apnea, undescended testes, metabolic acidosis, central hypotonia, wrist and finger contractures, club foot, diminished reflexes, hypertonia, and spasticity.
BP7			Missense variant is non-synonymous
BP4			Multiple lines of computational evidence support a deleterious effect
BP3			Missense variant
BP1			Missense variants in ACTA1 are associated with pathogenicity therefore BP1 is not applicable to variants in ACTA1
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1		✖	No pathogenic variants in the same codon causing the same amino acid change has been identified
PS3		✖	No functional studies of variant available.
PS4		✖	Only one patient reported by ARUP lab was scorable. PMID: 19562689 discusses one proband with NMR without additional phenotype or inheritance information, and was not scored.
BA1		✖	Absent from gnomAD, ExAC, and 1000 Genomes
PP1		✖	Segregation data not available
PP4		✖	Patient phenotype as reported by ARUP as the following: "infant had distal arthrogryposis, central apnea, undescended testes, metabolic acidosis, central hypotonia, wrist and finger contractures, club foot, diminished reflexes, hypertonia and spasticity." In PMID: 19562689 patient with variant was diagnosed with NMR.
PM6		✖	Paternity and maternity confirmed
PM1		✖	There are no mutational hot spots in ACTA1 per VCEP guidance and PMID: 19562689
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	NM_001100.4(ACTA1):c.39C>A (p.Asp13Glu) has been interpreted as pathogenic by LabCorp in ClinVar, yet VUS by GeneDx and there does not seem to be sufficient evidence in the literature to interpret this variant as pathogenic by ClinGen standards therefore, I do not feel PM5 can be invoked in this case.
PM4		✖	Missense variant

Curation History 



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