

Variant: *NM_000277.2(PAH):c.140C>T (p.Ala47Val)*

Version: 1.0

CA114370 [↗](#)

630 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: b16a5fd2-c502-44ff-a982-59b607e2ca9b

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HGVS expressions

NM_000277.2:c.140C>T

NM_000277.2(PAH):c.140C>T (p.Ala47Val)

NC_000012.12:g.102912819G>A

CM000674.2:g.102912819G>A

NC_000012.11:g.103306597G>A

CM000674.1:g.103306597G>A

NC_000012.10:g.101830727G>A

NG_008690.1:g.9784C>T

NG_008690.2:g.50592C>T

ENST00000553106.6:c.140C>T

ENST00000307000.7:c.125C>T

ENST00000546844.1:c.140C>T

ENST00000548677.2:n.227C>T

ENST00000548928.1:n.62C>T

ENST00000549111.5:n.236C>T

ENST00000550978.6:c.124C>T

ENST00000551337.5:c.140C>T

ENST00000551988.5:n.229C>T

ENST00000553106.5:c.140C>T

ENST00000635500.1:n.108C>T

NM_000277.1:c.140C>T

NM_001354304.1:c.140C>T

NM_000277.3:c.140C>T

NM_001354304.2:c.140C>T

Likely Pathogenic

Met criteria codes 3

PP4_Moderate

PM3_Strong

PM2

Not Met criteria codes 2

PP3

PS3

Evidence Links 5

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Phenylketonuria VCEP

The c.140C>T (p.Ala47Val) variant in PAH has been reported in 3 individuals with MHP (BH4 deficiency excluded). (PMID: 24368688, 27121329). This variant has extremely low frequency in gnomAD MAF=0.00001. This variant was detected with pathogenic variants p.E280K (parental analysis not reported), p.Glu178Gly, c.1066-11G>A (segregation analysis done). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong.

Met criteria codes

PP4_Moderate			A47V in 2 patients with MHP phenylalanine levels <360 umol/liter. A defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels and dihydropteridine reductase activity. PMID: 27121329
PubMed:27121329  PubMed:23514811  In Appdenxi, A47V classified as MHP variant PubMed:9634518 			
PM3_Strong			p.E280K (P 9 submitters) parental analysis not reported PMID: 24368688 p.Glu178Gly (P 6 submitters) c.1066-11G>A (P 7 submitters) segregation analysis done PMID: 27121329
PubMed:24368688 			
PM2			extremely low frequency in GnomAD MAF=0.00001

Not Met criteria codes

PP3			Conflicting predictions of pathogenicity: SIFT-D Polyphen2-B MutationTaster-D REVEL=0.797
PS3			PMID 11326337: Binding studies showed that the wild-type form specifically binds phenylalanine, whereas A47V abolished or significantly reduced this phenylalanine-binding capacity.
To examine whether N-terminal PAH mutations affect the ability of PAH to bind phenylalanine at the regulatory domain, wild-type and five mutant (G46S, A47V, T63P/H64N, I65T, and R68S) forms of the N-terminal domain (residues 2-120) of human PAH were expressed as fusion proteins in Escherichia coli. Binding studies showed that the wild-type form of this domain specifically binds phenylalanine, whereas all mutations abolished or significantly reduced this phenylalanine-binding capacity. PubMed:11326337 			

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