

Variant: *NM_000277.3(PAH):c.439C>T (p.Pro147Ser)*

Version: 1.0

CA229541 [↗](#)

102669 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e9f34e4e-66a8-4bb8-bb23-91567aa6569a

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HGVS expressions

NM_000277.3:c.439C>T

NM_000277.3(PAH):c.439C>T (p.Pro147Ser)

NC_000012.12:g.102877464G>A

CM000674.2:g.102877464G>A

NC_000012.11:g.103271242G>A

CM000674.1:g.103271242G>A

NC_000012.10:g.101795372G>A

NG_008690.1:g.45139C>T

NG_008690.2:g.85947C>T

ENST00000553106.6:c.439C>T

ENST00000307000.7:c.424C>T

ENST00000549111.5:n.535C>T

ENST00000550978.6:c.423C>T

ENST00000551988.5:n.528C>T

ENST00000553106.5:c.439C>T

NM_000277.1:c.439C>T

NM_000277.2:c.439C>T

NM_001354304.1:c.439C>T

NM_001354304.2:c.439C>T

Likely Pathogenic

Met criteria codes 4

PP4_Moderate

PM3_Strong

PP3

PM2

Not Met criteria codes 1

PM5

Evidence Links 4

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.439C>T (p.Pro147Ser) variant in PAH was reported in at least 5 patients with PAH deficiency, detected with pathogenic variants p.Arg243Gln (PMID: 27121329), p.S349P (PMID: 15589814), c.1045T>C, c.782G>A (PMID: 24941924) and p.A403V (PMID: 10234516). DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia (PMID: 27121329). This variant is present at an extremely low frequency in gnomAD (MAF=0.00003). Computational evidence for this missense variant supports a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PP4_moderate, PP3.

Met criteria codes

PP4_Moderate			PP4_moderate: Detected in a patient with classical PKU. A defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity. PMID: 27121329
PubMed:27121329 			
PM3_Strong			PM3_strong: This variant was detected in trans with pathogenic variants in 4 classic PKU patients and 1 mild hyperphenylalaninemia (MHP) patient (PMID: 27121329, 15589814, 24941924, 10234516). 27121329 - This variant was detected in trans with the pathogenic PAH variant p.Arg243Gln in 1 patient with classic phenylketonuria, and parental analysis was performed to confirm compound heterozygosity. 15589814 - This variant was detected in trans with the pathogenic variant S349P in 1 patient with classic phenylketonuria. Parental analysis was not performed to confirm compound heterozygosity. 24941924 - This variant was detected in trans with the pathogenic PAH variant c.1045T>C (7 pathogenic submissions in ClinVar, 1 likely pathogenic) in 1 patient with classic phenylketonuria. This variant was also detected in trans with the pathogenic PAH variant c.782G>A in 1 patient with classic phenylketonuria. Familial segregation analysis was confirmed in most patients, but it was unclear whether segregation analysis was performed for these patients. 10234516 - This variant was detected in trans with the pathogenic PAH variant A403V in at least 1 patient with mild hyperphenylalanemia (MHP). Mendelian inheritance was confirmed when parental samples were available by DGGE or restriction enzyme digestion, but it is unclear whether parental analysis was performed to confirm compound heterozygosity in this case.
PubMed:24941924 			
PubMed:10234516 			
PubMed:15589814 			
PP3			PP3_met: predicted deleterious in SIFT, Polyphen2, mutationTaster, REVEL=0.96
PM2			PM2_met: Extremely low frequency in gnomAD (MAF=0.00003)

Not Met criteria codes

PM5			PM5_not met: P147L is interpreted as LP by PAH VCEP/ClinVar
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Curation History 

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