

Variant: *NM_000277.1(PAH):c.1181A>C (p.Asp394Ala)*

Version: 1.0

CA229372 [↗](#)

102546 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7a9bcf99-ca91-4187-90e5-ee51bdab6bfa

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HGVS expressions

NM_000277.1:c.1181A>C

NM_000277.1(PAH):c.1181A>C (p.Asp394Ala)

NC_000012.12:g.102843664T>G

CM000674.2:g.102843664T>G

NC_000012.11:g.103237442T>G

CM000674.1:g.103237442T>G

NC_000012.10:g.101761572T>G

NG_008690.1:g.78939A>C

NG_008690.2:g.119747A>C

ENST00000553106.6:c.1181A>C

ENST00000307000.7:c.1166A>C

ENST00000549247.6:n.940A>C

ENST00000551114.2:n.843A>C

ENST00000553106.5:c.1181A>C

ENST00000635477.1:c.285A>C

ENST00000635528.1:n.696A>C

NM_000277.2:c.1181A>C

NM_001354304.1:c.1181A>C

NM_000277.3:c.1181A>C

NM_001354304.2:c.1181A>C

Likely Pathogenic

Met criteria codes **4**

PP3

PM3

PM2

PP4_Moderate

Not Met criteria codes **1**

PM5

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1181A>C (p.Asp394Ala) variant in PAH has been reported in multiple Sicilian individuals with PAH deficiency (BH4 deficiency excluded, PMID: 8268925). This variant is absent in population databases. This variant was detected with pathogenic variants: p.R261Q (PMID: 8830172); IVS4+5G>T (PMID: 21837404). Computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP3			Predicted deleterious in SIFT, Polyphen2, MutationTaster, REVEL=0.93
PM3			Found with R261Q, which is pathogenic 11 submitters in ClinVar parental testing not reported PMID: 8830172; in trans with IVS4+5G>T (confirmed by testing in offspring) P 7 submitters PMID: 21837404
Family F32, genotype R261Q/D394A. R261Q (VarID 582, Pathogenic/LP in ClinVar) PubMed:8830172 			
PM2			Absent from SIFT, gnomAD, 1000G, ESP
PP4_Moderate			D394A seen in 1 patient with blood phe (313 umol/L). Other causes of hyperphenylalaninemia were ruled out with normal urinary excretion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. PMID: 8268925
53 unrelated patients presenting with blood phenylalanine levels persistently above 150 /umol/l. Diagnosis of PAH deficiency was made when other potential causes of hyperphenylalaninemia had been ruled out The criteria for inclusion were: normal serum tyrosine, normal urinary excretion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. D394A seen on 1 allele. PubMed:8268925 			

Not Met criteria codes

PM5			Asp394Tyr and His likely pathogenic based on 1 submission each in ClinVar
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Curation History

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