The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.940C>A (p.Pro314Thr)

Version: 1.0

CA229863

102904 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2c9b39fe-5280-4908-8231-1042d91c7fac
Approved on: 2023/12/30
Published on: 2023/12/30

HGVS expressions

NM_000277.1:c.940C>A
NM_000277.1(PAH):c.940C>A (p.Pro314Thr)
NC_000012.12:g.102846924G>T
CM000674.2:g.102846924G>T
NC_000012.11:g.103240702G>T
CM000674.1:g.103240702G>T
NC_000012.10:g.101764832G>T
NG_008690.1:g.75679C>A
NG_008690.2:g.116487C>A
ENST00000553106.6:c.940C>A
ENST00000307000.7:c.925C>A
ENST00000549247.6:n.699C>A
ENST00000551114.2:n.602C>A
ENST00000553106.5:c.940C>A
ENST00000635477.1:c.74-2493C>A
ENST00000635528.1:n.455C>A
NM_000277.2:c.940C>A
NM_001354304.1:c.940C>A
NM_000277.3:c.940C>A
NM_001354304.2:c.940C>A

Pathogenic

Met criteria codes 4

PM3_Very Strong | PS3_Supporting | PM2_Supporting | PP4_Moderate

Not Met criteria codes 4

BA1 | BS1 | BS3 | PP3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.1(PAH):c.940C>A (p.Pro314Thr) variant is a missense variant in exon 9/13 of PAH. It has been found to result in 25% of wild-type PAH enzyme activity in a standard cDNA system and 19% of wild-type PAH enzyme activity in an Intinc system (PMID: 18590700) (PS3_supporting). It has been reported in at least five PKU patients, including those with BH4 deficiency excluded and in trans with Pathogenic variants (PM3_VeryStrong (4.25 points); PP4_Moderate). It has been previously reported in a Taiwanese proband in trans with p.V399V (Pathogenic in ClinVar and per ClinGen PAH VCEP) with mild hyperphenylalanemia and BH4 deficiency excluded by urinary pterins, dihydropteridine reductase activity in erythrocytes, and sequencing of the genes in the BH4 cofactor metabolism pathway (PMID: 14722928). It has also been found in trans with p.V399V (Pathogenic in ClinVar and per ClinGen PAH VCEP) in a Chinese patient with classic PKU (plasma Phe 1230 umol/L) and BH4 deficiency excluded (PMID: 28982351). It has been noted in a Chinese patient with plasma Phe 184 umol/L and BH4 deficiency excluded in trans with a deletion of exons 1-3 (unclassified) (PMID: 29499199). It has been also noted in a Chinese patient with mild hyperphenylalanemia (plasma Phe 148 umol/L) in trans with the p.S70del (Pathogenic in ClinVar and per ClinGen PAH VCEP) variant and in trans with the p.R243Q (Pathogenic in ClinVar and per ClinGen PAH VCEP) variant in a patient with classic PKU (plasma Phe 1561 umol/L); BH4 deficiency was excluded in both cases (PMID: 30459323). Another missense variant at the same site, c.941C>A (p.P314H) is classified as Pathogenic/Likely Pathogenic in ClinVar (ID 102907) (PM5). Two heterozygotes and zero homozygotes for the variant are present in gnomAD, corresponding to a global frequency of 0.00000796 and a maximum population frequency of 0.000109 (South Asian), under the 0.0002 frequency cutoff for use of PM2 (PM2_supporting). The variant is predicted damaging by multiple in-silico predictors, including REVEL (REVEL score 0.867), but tolerated by SIFT; thus, PP3 is not met. Classification: Pathogenic Supporting Criteria: PS3_supporting; PM3_VeryStrong; PM2_supporting; PP4_Moderate

Met criteria codes

PM3_Very Strong ✔

It has been reported in at least five PKU patients, including those with BH4 deficiency excluded and in trans with Pathogenic variants (PM3_VeryStrong (4.25 points); PP4_Moderate). It has been previously reported in a Taiwanese proband in trans with p.V399V (Pathogenic in ClinVar and per ClinGen PAH VCEP) with mild hyperphenylalanemia and BH4 deficiency excluded by urinary pterins, dihydropteridine reductase activity in erythrocytes, and sequencing of the genes in the BH4 cofactor metabolism pathway (PMID: 14722928). It has also been found in trans with p.V399V (Pathogenic in ClinVar and per ClinGen PAH VCEP) in a Chinese patient with classic PKU (plasma Phe 1230 umol/L) and BH4 deficiency excluded (PMID: 28982351). It has been noted in a Chinese patient with plasma Phe 184 umol/L and BH4 deficiency excluded in trans with a deletion of exons 1-3 (unclassified) (PMID: 29499199). It has been also noted in a Chinese patient with mild hyperphenylalanemia (plasma Phe 148 umol/L) in trans with the p.S70del (Pathogenic in ClinVar and per ClinGen PAH VCEP) variant and in trans with the p.R243Q (Pathogenic in ClinVar and per ClinGen PAH VCEP) variant in a patient with classic PKU (plasma Phe 1561 umol/L); BH4 deficiency was excluded in both cases (PMID: 30459323).

Taiwanese population, novel mutation in this paper. Single patient with 185uM phe at dx. PubMed:14722928

PS3_Supporting ✔

It has been found to result in 25% of wild-type PAH enzyme activity in a standard cDNA system and 19% of wild-type PAH enzyme activity in an Intinc system (PMID: 18590700) (PS3).

PM2_Supporting ✔

Two heterozygotes and zero homozygotes for the variant are present in gnomAD, corresponding to a global frequency of 0.00000796 and a maximum population frequency of 0.000109 (South Asian), under the 0.0002 frequency cutoff for use of PM2 (PM2).

PP4_Moderate ✔

BH4 defect excluded in all patients (Liang 2014). Single patient with phe 185uM at dx (Chien 2004)

Taiwanese patients. Patient #24 PubMed:14722928
Taiwanese patients, single patient, possibly overlap with Chien 2004 paper. BH4 defect excluded in all patients PubMed:24401910

Not Met criteria codes

BA1	✖	Two heterozygotes and zero homozygotes for the variant are present in gnomAD, corresponding to a global frequency of 0.00000796 and a maximum population frequency of 0.000109 (South Asian), under the 0.0002 frequency cutoff for use of PM2 (PM2).
BS1	✖	Two heterozygotes and zero homozygotes for the variant are present in gnomAD, corresponding to a global frequency of 0.00000796 and a maximum population frequency of 0.000109 (South Asian), under the 0.0002 frequency cutoff for use of PM2 (PM2).
BS3	✖	It has been found to result in 25% of wild-type PAH enzyme activity in a standard cDNA system and 19% of wild-type PAH enzyme activity in an Intinc system (PMID: 18590700) (PS3).
PP3	✖	SIFT predicts tolerated, others predict damaging. REVEL=0.867

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.