

Variant: *NM_000277.1(PAH):c.922C>T (p.Leu308Phe)*

Version: 1.0

CA229851 [↗](#)

102896 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e354abcd-4638-45fa-94a7-21c6c430ddb4

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HGVS expressions

NM_000277.1(PAH):c.922C>T (p.Leu308Phe)

NM_000277.1:c.922C>T

NC_000012.12:g.102846942G>A

CM000674.2:g.102846942G>A

NC_000012.11:g.103240720G>A

CM000674.1:g.103240720G>A

NC_000012.10:g.101764850G>A

NG_008690.1:g.75661C>T

NG_008690.2:g.116469C>T

ENST00000553106.6:c.922C>T

ENST00000307000.7:c.907C>T

ENST00000549247.6:n.681C>T

ENST00000551114.2:n.584C>T

ENST00000553106.5:c.922C>T

ENST00000635477.1:c.74-2511C>T

ENST00000635528.1:n.437C>T

NM_000277.2:c.922C>T

NM_001354304.1:c.922C>T

NM_000277.3:c.922C>T

NM_001354304.2:c.922C>T

Pathogenic

Met criteria codes **4**

PM2_Supporting

PP4_Moderate

PM3_Very Strong

PP3

Not Met criteria codes **1**

PS3

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen PAH Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines Version 1

[↗](#) **Criteria Specification Approval History**

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

Phenylketonuria VCEP

The NM_000277.1(PAH):c.922C>T (p.Leu308Phe) variant is a missense variant in exon 9/13 of PAH. The variant has been found to lead to 47% of wild-type enzyme activity in an intron-included (Intinc) system (PMID: 18590700) and is listed as having 49% of wild-type enzyme activity in BioPKU (ID PAH0362), consistent with a published report in a prokaryotic system (PMID: 16091306; PMID: 15557004). It has been found in at least seven PKU patients, including in trans with other Pathogenic or Likely Pathogenic variants and among patients with BH4 deficiency excluded (PM3_VeryStrong (6 points total); PP4_Moderate). It has been found in trans with the p.R261Q variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) in a patient with classic PKU (plasma Phe >1200 umol/L) with BH4 deficiency excluded by urine pterin profile and blood dihydropteridine reductase (DHPR) activity (PMID: 15557004; PMID: 14726806). It has been found in a Chinese patient with plasma Phe 467 umol/L and BH4 deficiency excluded by urinary pterin analysis and DHPR activity assay, in trans with a deletion of exon 1 (unclassified variant) (PMID: 29499199). It has also been noted in at least 3 Swedish PKU patients detected by NBS (PMID: 27469133). The variant has been previously reported in 3 Chinese PKU patients with BH4 deficiency excluded by dihydropteridine reductase activity, urinary biopterin and neopterin ratio: one with mild hyperphenylalanemia in trans with p.S70del (Pathogenic in ClinVar and by ClinGen PAH VCEP); one with mild PKU in trans with p.Q232* (Pathogenic in ClinVar); and one with mild PKU in trans with with c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been noted in 2 Czech patients with mild PKU, one with p.R252W and one with p.P281L; neither parental testing or exclusion of BH4 deficiency were noted (PMID: 23357515). The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2_supporting). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.892) (PP3).

Met criteria codes

PM2_Supporting			Not found in any population databases
PP4_Moderate			It has been found in at least seven PKU patients, including in trans with other Pathogenic or Likely Pathogenic variants and among patients with BH4 deficiency excluded (PM3_VeryStrong (6 points total); PP4_Moderate). It has been found in trans with the p.R261Q variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) in a patient with classic PKU (plasma Phe >1200 umol/L) with BH4 deficiency excluded by urine pterin profile and blood dihydropteridine reductase (DHPR) activity (PMID: 15557004; PMID: 14726806). It has been found in a Chinese patient with plasma Phe 467 umol/L and BH4 deficiency excluded by urinary pterin analysis and DHPR activity assay, in trans with a deletion of exon 1 (unclassified variant) (PMID: 29499199). It has also been noted in at least 3 Swedish PKU patients detected by NBS (PMID: 27469133). The variant has been previously reported in 3 Chinese PKU patients with BH4 deficiency excluded by dihydropteridine reductase activity, urinary biopterin and neopterin ratio: one with mild hyperphenylalanemia in trans with p.S70del (Pathogenic in ClinVar and by ClinGen PAH VCEP); one with mild PKU in trans with p.Q232* (Pathogenic in ClinVar); and one with mild PKU in trans with with c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been noted in 2 Czech patients with mild PKU, one with p.R252W and one with p.P281L; neither parental testing or exclusion of BH4 deficiency were noted (PMID: 23357515).

Patient cohort from Children's Hospital of L.A. and University of Texas at Galveston. All patients had normal urine pterin profile and normal DHPR activity. [PubMed:14726806](#) 

PM3_Very Strong			It has been found in at least seven PKU patients, including in trans with other Pathogenic or Likely Pathogenic variants and among patients with BH4 deficiency excluded (PM3_VeryStrong (6 points total); PP4_Moderate). It has been found in trans with the p.R261Q variant (Pathogenic in ClinVar and by ClinGen PAH VCEP) in a patient with classic PKU (plasma Phe >1200 umol/L) with BH4 deficiency excluded by urine pterin profile and blood dihydropteridine reductase (DHPR) activity (PMID: 15557004; PMID: 14726806). It has been found in a Chinese patient with plasma Phe 467 umol/L and BH4 deficiency excluded by urinary pterin analysis and DHPR activity assay, in trans with a deletion of exon 1 (unclassified variant) (PMID: 29499199). It has also been noted in at least 3 Swedish PKU patients detected by NBS (PMID: 27469133). The variant has been previously reported in 3 Chinese PKU patients with BH4 deficiency excluded by dihydropteridine reductase activity, urinary biopterin and neopterin
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ratio: one with mild hyperphenylalanemia in trans with p.S70del (Pathogenic in ClinVar and by ClinGen PAH VCEP); one with mild PKU in trans with p.Q232* (Pathogenic in ClinVar); and one with mild PKU in trans with with c.442-1G>A (Pathogenic in ClinVar and by ClinGen PAH VCEP) (PMID: 30050108). It has been noted in 2 Czech patients with mild PKU, one with p.R252W and one with p.P281L; neither parental testing or exclusion of BH4 deficiency were noted (PMID: 23357515).

PP3



All databases agree on damaging effect. REVEL score 0.892

Not Met criteria codes

PS3



Ho et.al 2008, 47% enzyme activity in intron-included (intinic) system--suggests this variant leads to exon 9 skipping. BioPKU states 49% enzyme activity.

PAH activity analysis. Site directed mutagenesis, transfected COS-1 cells. Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. Use both standard cDNA expression system and a new Intinic plasmid system which incorporates intronic sequences. Standard cDNA method demonstrates 78% and intinic system demonstrates 47% residual enzyme activity. Suggests exon 9 skipping. [PubMed:18590700](#) 

Curation History

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