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:c.971T>A

Version: 1.0

CA10602335

2682170 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 43243d0e-d5fb-4550-9585-d6c1913c3448
Approved on: 2023/12/30
Published on: 2023/12/30

HGVS expressions

NM_000277.1:c.971T>A
NC_000012.12:g.102844430A>T
CM000674.2:g.102844430A>T
NC_000012.11:g.103238208A>T
CM000674.1:g.103238208A>T
NC_000012.10:g.101762338A>T
NG_008690.1:g.78173T>A
NG_008690.2:g.118981T>A
ENST00000553106.6:c.971T>A
ENST00000307000.7:c.956T>A
ENST00000549247.6:n.730T>A
ENST00000551114.2:n.633T>A
ENST00000553106.5:c.971T>A
ENST00000635477.1:c.75T>A
ENST00000635528.1:n.486T>A
NM_000277.2:c.971T>A
NM_001354304.1:c.971T>A
NM_000277.3:c.971T>A
NM_001354304.2:c.971T>A

Pathogenic

Met criteria codes 4

PM3_Very Strong | PP4_Moderate | PP3 | PM2_Supporting

Not Met criteria codes 1

PS3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.3:c.971T>A (p.Ile324Asn) variant is a missense variant in exon 10 of 13 of PAH. It has been previously reported in at least 12 patients with PKU and BH4 deficiency formally excluded, including in confirmed trans with Pathogenic or Likely Pathogenic variants (PM3_VeryStrong (7.5 points total); PP4_Moderate). It was reported in presumed trans with p.R241C (Pathogenic per ClinGen PAH VCEP) in a Chinese proband with mild PKU (plasma Phe 760 µmol/L) and BH4 deficiency was said to be excluded (PMID: 28982351); in presumed trans with p.R111* (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU and in presumed trans with c.509+1G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU (plasma Phe levels not specified; BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes). It has also been reported in confirmed trans with c.1066-11G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with PKU and BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 24705691); in a Chinese proband with PKU in confirmed trans with the c.442–1G>A variant (Pathogenic by ClinGen PAH VCEP) and in another Chinese proband with PKU in confirmed trans with the p.G247R variant (Likely Pathogenic by ClinGen PAH VCEP) (PMID: 29353259). It has been noted in a patient with PKU in presumed trans with p.T418P variant (Pathogenic by ClinGen PAH VCEP) (plasma Phe levels not noted; BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 29731766); in a Chinese patient with mild PKU (plasma Phe 780 umol/L) in presumed trans with the p.R243Q variant (Pathogenic by ClinGen PAH VCEP) and BH4 deficiency excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 28754886). Finally, it has been noted among multiple Chinese PKU patients with BH4 deficiency excluded by urinary pterin analysis, including in the homozygous state in a Chinese patient with classic PKU (plasma Phe not noted), in another patient with PKU (phenotype not further specified) in presumed trans with the c.611A>G (p.Ex6-96A>G) variant (Pathogenic by ClinGen PAH VCEP), in presumed trans with the p.V399V variant (Pathogenic by ClinGen PAH VCEP) in another Chinese patient with mild PKU, and in presumed trans with the p.Y356* variant (Pathogenic by ClinGen PAH VCEP) (PMID: 30050108). 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 0.889) (PP3). Classification: Pathogenic Supporting Criteria: PM3_VeryStrong; PM2_supporting; PP4_Moderate; PP3

Met criteria codes

PM3_Very Strong ✔

It has been previously reported in at least 12 patients with PKU and BH4 deficiency formally excluded, including in confirmed trans with Pathogenic or Likely Pathogenic variants (PM3_VeryStrong (7.5 points total); PP4_Moderate). It was reported in presumed trans with p.R241C (Pathogenic per ClinGen PAH VCEP) in a Chinese proband with mild PKU (plasma Phe 760 µmol/L) and BH4 deficiency was said to be excluded (PMID: 28982351); in presumed trans with p.R111* (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU and in presumed trans with c.509+1G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU (plasma Phe levels not specified; BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes). It has also been reported in confirmed trans with c.1066-11G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with PKU and BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 24705691); in a Chinese proband with PKU in confirmed trans with the c.442–1G>A variant (Pathogenic by ClinGen PAH VCEP) and in another Chinese proband with PKU in confirmed trans with the p.G247R variant (Likely Pathogenic by ClinGen PAH VCEP) (PMID: 29353259). It has been noted in a patient with PKU in presumed trans with p.T418P variant (Pathogenic by ClinGen PAH VCEP) (plasma Phe levels not noted; BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 29731766); in a Chinese patient with mild PKU (plasma Phe 780 umol/L) in presumed trans with the p.R243Q variant (Pathogenic by ClinGen PAH VCEP) and BH4 deficiency excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 28754886). Finally, it has been noted among multiple Chinese PKU patients with BH4 deficiency excluded by urinary pterin analysis, including in the homozygous state in a Chinese patient with classic PKU (plasma Phe not noted), in another patient with PKU (phenotype not further specified) in presumed trans with the c.611A>G (p.Ex6-96A>G) variant (Pathogenic by ClinGen PAH VCEP), in presumed trans with the p.V399V variant (Pathogenic by ClinGen PAH VCEP) in another Chinese patient with mild PKU, and in presumed trans with the p.Y356* variant (Pathogenic by ClinGen PAH VCEP) (PMID: 30050108).

Patient #7 I324N / R243Q with moderate PKU (720-780umol/L Phe) **PubMed:24327145**
Single patient with this allele c.971T>A / c.331C>T (R111*) pathogenic with "classic PKU", but no specific Phe levels listed. **PubMed:26322415**

PP4_Moderate	ℹ	✔	It has been previously reported in at least 12 patients with PKU and BH4 deficiency formally excluded, including in confirmed trans with Pathogenic or Likely Pathogenic variants (PM3_VeryStrong (7.5 points total); PP4_Moderate). It was reported in presumed trans with p.R241C (Pathogenic per ClinGen PAH VCEP) in a Chinese proband with mild PKU (plasma Phe 760 µmol/L) and BH4 deficiency was said to be excluded (PMID: 28982351); in presumed trans with p.R111* (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU and in presumed trans with c.509+1G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with classic PKU (plasma Phe levels not specified; BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes). It has also been reported in confirmed trans with c.1066-11G>A (Pathogenic by ClinGen PAH VCEP) in a Chinese proband with PKU and BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 24705691); in a Chinese proband with PKU in confirmed trans with the c.442–1G>A variant (Pathogenic by ClinGen PAH VCEP) and in another Chinese proband with PKU in confirmed trans with the p.G247R variant (Likely Pathogenic by ClinGen PAH VCEP) (PMID: 29353259). It has been noted in a patient with PKU in presumed trans with p.T418P variant (Pathogenic by ClinGen PAH VCEP) (plasma Phe levels not noted; BH4 deficiency excluded by sequencing of genes in the BH4 cofactor metabolism pathway) (PMID: 29731766); in a Chinese patient with mild PKU (plasma Phe 780 umol/L) in presumed trans with the p.R243Q variant (Pathogenic by ClinGen PAH VCEP) and BH4 deficiency excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 28754886). Finally, it has been noted among multiple Chinese PKU patients with BH4 deficiency excluded by urinary pterin analysis, including in the homozygous state in a Chinese patient with classic PKU (plasma Phe not noted), in another patient with PKU (phenotype not further specified) in presumed trans with the c.611A>G (p.Ex6-96A>G) variant (Pathogenic by ClinGen PAH VCEP), in presumed trans with the p.V399V variant (Pathogenic by ClinGen PAH VCEP) in another Chinese patient with mild PKU, and in presumed trans with the p.Y356* variant (Pathogenic by ClinGen PAH VCEP) (PMID: 30050108). BH4 defect excluded with urine pterins and DHPR activity. Single patient with this variant. PubMed:26322415 BH4 defect excluded via sequencing of all genes associated with primary BH4 defects. Single patient PubMed:24705691
PP3	ℹ	✔	All computational evidence suggests damaging effect. REVEL=0.889
PM2_Supporting	ℹ	✔	Not found in gnomAD v2.1.1

Not Met criteria codes

PS3	✖	In vitro expression analysis shows PAH activity of 50.6% PMID: 24327145 In vitro expression analysis shows PAH activity of 50.6% PubMed:24327145

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.