

Variant: *NM_000277.1(PAH):c.964G>A (p.Ala322Thr)*

Version: 1.0

CA229875 [↗](#)

102912 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7039f3bd-2b3c-4ee5-ad2f-78223d9e2416

Approved on: 2023/12/30

Published on: 2023/12/30

HGVS expressions

NM_000277.1(PAH):c.964G>A (p.Ala322Thr)

NM_000277.1:c.964G>A

NC_000012.12:g.102846900C>T

CM000674.2:g.102846900C>T

NC_000012.11:g.103240678C>T

CM000674.1:g.103240678C>T

NC_000012.10:g.101764808C>T

NG_008690.1:g.75703G>A

NG_008690.2:g.116511G>A

ENST00000553106.6:c.964G>A

ENST00000307000.7:c.949G>A

ENST00000549247.6:n.723G>A

ENST00000551114.2:n.626G>A

ENST00000553106.5:c.964G>A

ENST00000635477.1:c.74-2469G>A

ENST00000635528.1:n.479G>A

NM_000277.2:c.964G>A

NM_001354304.1:c.964G>A

NM_000277.3:c.964G>A

NM_001354304.2:c.964G>A

Pathogenic

Met criteria codes 4

PM3_Very Strong

PP3

PP4_Moderate

PS3_Supporting

Not Met criteria codes 4

PM5

PM2

BA1

BS1

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.964G>A (p.Ala322Thr) variant is a missense variant in exon 9/13 of PAH. The variant has been found to reduce PAH enzymatic activity to 11% of wild-type in an Intinc system and 20% of wild-type in a cDNA system in transfected cells (PMID: 18590700) (PS3_supporting). The variant has been previously noted in at least four PKU patients among whom BH4 deficiency was excluded, including in trans with Pathogenic or Likely Pathogenic alleles (PM3_VeryStrong (4 points); PP4_Moderate). The variant has been previously reported in a Chinese patient with mild hyperphenylalanemia in trans with the p.R111* variant (Pathogenic in ClinVar and by the ClinGen PAH VCEP); BH4 deficiency was excluded via analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PMID: 30050108; PMID: 26322415). It has been noted in a Spanish patient with mild hyperphenylalanemia in trans with the p.S349P variant (Pathogenic in ClinVar and by the ClinGen PAH VCEP); BH4 deficiency was excluded analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity (PMID: 27121329). It was found in a Slovak patient with mild hyperphenylalanemia in trans with the p.A403V variant (Pathogenic in ClinVar and by the ClinGen PAH VCEP); BH4 deficiency was excluded (PMID: 23764561). It has been noted in a Chinese patient with PKU (plasma Phe >120 umol/L; no further specification) and BH4 deficiency excluded in trans with p.R176* (Pathogenic in ClinVar and by the ClinGen PAH VCEP) (PMID: 26600521). Another missense variant at the same site, p.A322G, is classified Pathogenic in ClinVar (ID 616) and by the ClinGen PAH VCEP. 18 heterozygotes and zero homozygotes are present for the variant in gnomAD, corresponding to a global frequency of 0.0000716 and a maximum population frequency of 0.000261; these frequencies exceed the 0.0002 cutoff for use of PM2, but is lower than the 0.002 cutoff for use of BS1. The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.889) (PP3). Classification: Pathogenic Supporting Criteria: PS3_supporting; PM3_VeryStrong; PP4_Moderate; PP3

Met criteria codes

PM3_Very Strong



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147 patients. A single patient with this variant c.964G>A (p.A322T) / c.331C>T (pR111X) (pathogenic) with mild hyperphenylalanemia (Phe <10mg/dL) Methods – All patients were picked up by NBS and BH4 defect was excluded in all patients with urine pterins and DHPR activity. [PubMed:26322415](#)

PP3



All computational evidence support a deleterious effect on gene product. REVEL=0.889

PP4_Moderate



BH4 defect was excluded in all patients with urine pterins and DHPR activity.

147 patients. A single patient with this variant c.964G>A (p.A322T) / c.331C>T (pR111X) (pathogenic) with mild hyperphenylalanemia (Phe <10mg/dL) Methods – All patients were picked up by NBS and BH4 defect was excluded in all patients with urine pterins and DHPR activity. [PubMed:26322415](#)

PS3_Supporting



Standard cDNA method demonstrates 20% and intinic system demonstrates 11% residual 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 20% and intinic system demonstrates 11% residual enzyme activity [PubMed:18590700](#)

Not Met criteria codes

PM5			c.965C>G (Ala322Gly) pathogenic in ClinVar. Grantham score 60. Ala > Thr 58.
PM2			gnomAD v4: MAF of 0.0002197; exceeds the 0.0002 cutoff for use of PM2, but is lower than the 0.002 cutoff for use of BS1.
BA1			18 heterozygotes and zero homozygotes are present for the variant in gnomAD, corresponding to a global frequency of 0.0000716 and a maximum population frequency of 0.000261; these frequencies exceed the 0.0002 cutoff for use of PM2, but is lower than the 0.002 cutoff for use of BS1.
BS1			gnomAD v4: MAF of 0.0002197; exceeds the 0.0002 cutoff for use of PM2, but is lower than the 0.002 cutoff for use of BS1.

Curation History

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