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.941C>A (p.Pro314His)

Version: 1.0

CA229867

102907 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a3e4cda3-a69f-4eef-8f15-27c0a7fe9068
Approved on: 2023/12/30
Published on: 2023/12/30

HGVS expressions

NM_000277.1:c.941C>A
NM_000277.1(PAH):c.941C>A (p.Pro314His)
NC_000012.12:g.102846923G>T
CM000674.2:g.102846923G>T
NC_000012.11:g.103240701G>T
CM000674.1:g.103240701G>T
NC_000012.10:g.101764831G>T
NG_008690.1:g.75680C>A
NG_008690.2:g.116488C>A
ENST00000553106.6:c.941C>A
ENST00000307000.7:c.926C>A
ENST00000549247.6:n.700C>A
ENST00000551114.2:n.603C>A
ENST00000553106.5:c.941C>A
ENST00000635477.1:c.74-2492C>A
ENST00000635528.1:n.456C>A
NM_000277.2:c.941C>A
NM_001354304.1:c.941C>A
NM_000277.3:c.941C>A
NM_001354304.2:c.941C>A

Pathogenic

Met criteria codes 4

PM3_Very Strong | PM2_Supporting | PP3 | PP4_Moderate

Not Met criteria codes 2

PM5 | BS3

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**

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.1(PAH):c.941C>A (p.Pro314His) variant is a missense variant in exon 9/13 of PAH. It has been found to result in 15% of wild-type PAH enzyme activity in a standard cDNA system and 5% of wild-type PAH enzyme activity in an Intinc system (PMID: 18590700) (PS3_supporting). It has been noted in at least five patients, including in trans with Pathogenic or Likely Pathogenic variants and among those whom BH4 deficiency had been excluded (PM3_VeryStrong (4.25 points total); PP4_Moderate). It has been previously reported in a Mexican patient with mild hyperphenylalanemia in trans with the c.809G>A (p.Arg270Lys) variant (Pathogenic in ClinVar) (PMID: 24941924). It has been noted in 3 PKU patients: one in trans with the p.I94del variant (unclassified) and in two in trans with the p.Y277D variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 23842451). It has been found in a patient with mild hyperphenylalanemia (plasma Phe 456 umol/L) and BH4 deficiency excluded, in trans with the p.R155H variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 28593914). 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 0.91) (PP3). Classification: Pathogenic Supporting Criteria: PS3_supporting; PM2_supporting; PM3_VeryStrong; PP4_Moderate; PP3

Met criteria codes

PM3_Very Strong	✔	It has been noted in at least five patients, including in trans with Pathogenic or Likely Pathogenic variants and among those whom BH4 deficiency had been excluded (PM3_VeryStrong (4.25 points total); PP4_Moderate). It has been previously reported in a Mexican patient with mild hyperphenylalanemia in trans with the c.809G>A (p.Arg270Lys) variant (Pathogenic in ClinVar) (PMID: 24941924). It has been noted in 3 PKU patients: one in trans with the p.I94del variant (unclassified) and in two in trans with the p.Y277D variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 23842451). It has been found in a patient with mild hyperphenylalanemia (plasma Phe 456 umol/L) and BH4 deficiency excluded, in trans with the p.R155H variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 28593914). Retrospective study, large cohort of patients. Specific genotypes found in supplementary table 1. PubMed:23690520
PM2_Supporting	✔	Absent from all pop databases.
PP3	✔	All predictive software agree on damaging effect. REVEL=0.91
PP4_Moderate	✔	It has been noted in at least five patients, including in trans with Pathogenic or Likely Pathogenic variants and among those whom BH4 deficiency had been excluded (PM3_VeryStrong (4.25 points total); PP4_Moderate). It has been previously reported in a Mexican patient with mild hyperphenylalanemia in trans with the c.809G>A (p.Arg270Lys) variant (Pathogenic in ClinVar) (PMID: 24941924). It has been noted in 3 PKU patients: one in trans with the p.I94del variant (unclassified) and in two in trans with the p.Y277D variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 23842451). It has been found in a patient with mild hyperphenylalanemia (plasma Phe 456 umol/L) and BH4 deficiency excluded, in trans with the p.R155H variant (Pathogenic in ClinVar and per ClinGen PAH VCEP) (PMID: 28593914).

Not Met criteria codes

PM5	✖	two other variants (c.940C>T and 940C>A) are both VUS in ClinVar, but provisionally pathogenic in recent curation efforts
BS3	✖	

It has been found to result in 15% of wild-type PAH enzyme activity in a standard cDNA system and 5% of wild-type PAH enzyme activity in an Intinc system (PMID: 18590700) (PS3).

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 15% and intinic system demonstrates 5% residual enzyme activity. PubMed:18590700

Curation History

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