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# *Variant: NM_000277.2(PAH):c.125A>T (p.Lys42Ile)*

Version: 1.0

*CA229419*

*102581 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 295d33fe-390a-46a8-a5cf-dd0c34df16b9
**Approved on**: 2019-04-07
**Published on**: 2019-04-07

## *HGVS expressions*

**NM_000277.2:c.125A>T**
**NM_000277.2(PAH):c.125A>T (p.Lys42Ile)**
NC_000012.12:g.102912834T>A
CM000674.2:g.102912834T>A
NC_000012.11:g.103306612T>A
CM000674.1:g.103306612T>A
NC_000012.10:g.101830742T>A
NG_008690.1:g.9769A>T
NG_008690.2:g.50577A>T
NM_000277.1:c.125A>T
NM_001354304.1:c.125A>T
NM_000277.3:c.125A>T
ENST00000307000.7:c.110A>T
ENST00000546844.1:c.125A>T
ENST00000548677.2:n.212A>T
ENST00000548928.1:n.47A>T
ENST00000549111.5:n.221A>T
ENST00000550978.6:n.109A>T
ENST00000551337.5:c.125A>T
ENST00000551988.5:n.214A>T
ENST00000553106.5:c.125A>T
ENST00000635500.1:n.93A>T

**Likely Pathogenic**

**Met criteria codes** 4

PS3 PP4 PM2 PM3

**Not Met criteria codes** 1

PP3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.125A>T (p.Lys42Ile) variant in PAH has been reported in 1 individual with classic PKU (BH4 deficiency not assessed/reported). (PP4; PMID: 9380432; 9781015). This variant is absent in population databases (PM2). This variant was detected with p.E280K (Pathogenic in ClinVar) (PM3). This variant has 12% enzyme activity in vitro (PS3; PMID: 21953985). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3, PP4, PM2, PM3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✔ | 12% enzyme activity (PMID: 21953985)<br>We have applied a yeast two-hybrid method, in which protein--protein interactions are measured by four reporter gene constructs, to the analysis of six PKU-associated PAH missense mutations (F39L, K42I, L48S, I65T, A104D, and R157N). PubMed:11461190<br>p.K42I mutant had 12% total activity as compared to PAH wt. PubMed:21953985 |
| **PP4** | ✔ | detected in a patient with variant PKU (<1200 µmol/L) PMID: 9380432, 9781015<br>K42I occurred in a proband with classical PKU in a PAH genotype (K42I/E280K). PubMed:9781015<br>K42I was detected in a patient with variant PKU. Patients with variant PKU had pretreatment plasma phenylalanine values lower than those in PKU (<1200 µmol/L), and their dietary tolerance for phenylalanine was higher (>400 mg/d) but not normal. PubMed:9380432 |
| **PM2** | ✔ | Absent from ExAC/gnomAD, 1000 Genomes, ESP |
| **PM3** | ✔ | detected with E280K (VarID580, Pathogenic)<br>K42I, a novel mutation, and expressed in vivo with E280K (a so-called “severe” allele) confers a 6% oxidation value, implying that K42I is “mild”(Table 4). PubMed:9380432 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✖ | In silico models do not agree: D in SIFT, MutationTaster; B in PolyPhen2; REVEL=0.933 |

Curation History

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