

Variant: *NM\_000277.1:c.1249T>G*

Version: 1.0

CA16020982 [↗](#)

1327552 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 4c782a9b-194f-4bcf-b836-b7f74d93b474

**Approved on:** 2020/8/13

**Published on:** 2021/11/21

### HGVS expressions

**NM\_000277.1:c.1249T>G**

NC\_000012.12:g.102840466A>C

CM000674.2:g.102840466A>C

NC\_000012.11:g.103234244A>C

CM000674.1:g.103234244A>C

NC\_000012.10:g.101758374A>C

NG\_008690.1:g.82137T>G

NG\_008690.2:g.122945T>G

ENST00000553106.6:c.1249T>G

ENST00000307000.7:c.1234T>G

ENST00000551114.2:n.911T>G

ENST00000553106.5:c.1249T>G

ENST00000635477.1:c.353T>G

ENST00000635528.1:n.764T>G

NM\_000277.2:c.1249T>G

NM\_001354304.1:c.1249T>G

NM\_000277.3:c.1249T>G

NM\_001354304.2:c.1249T>G

**Likely Pathogenic**

Met criteria codes **4**

PP3

PP4

PM5

PM2

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

#### Phenylketonuria VCEP

The c.1249T>G (p.Tyr417Asp) variant in PAH has been reported in 1 individual with PAH deficiency (PMID: 10693064). This variant is absent in population databases. Computational evidence support a deleterious effect. Another missense variant at the same amino acid (p.Tyr417His) is interpreted as pathogenic. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM5, PP3, PP4.

| Met criteria codes                                                                                                |                                                                                   |                                                                                   |                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3                                                                                                               |  |  | Deleterious effect predicted in SIFT, PolyPhen2, MutationTaster, REVEL=0.991                                                                                     |
| PP4                                                                                                               |  |  | Y417D found on 1 allele of a hyperphenylalaninaemia patient. (normal values of blood phenylalanine <180 µmol/l). BH4 deficiency not investigated. PMID: 10693064 |
| 151 patients with hyperphenylalaninaemia originally from all of the Italian regions. Y417D was found on 1 allele. |                                                                                   |                                                                                   |                                                                                                                                                                  |
| PubMed:10693064                |                                                                                   |                                                                                   |                                                                                                                                                                  |
| PM5                                                                                                               |  |  | p.Tyr417His interpreted as pathogenic by 1 submitter and PAH VCEP                                                                                                |
| PM2                                                                                                               |                                                                                   |  | Absent from ExAC, gnomAD, 1000G, ESP                                                                                                                             |

| Curation History  |  |
|----------------------------------------------------------------------------------------------------|--|
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|                                                                                                    |  |

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