

Variant: NM\_001354304.2:c.361T>C

Version: 1.0

CA16020777 [↗](#)

2137411 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** ca01b22e-9d98-4c8c-af10-a21b38773412

**Approved on:** 2025/11/29

**Published on:** 2025/11/29

### HGVS expressions

**NM\_001354304.2:c.361T>C**

NC\_000012.12:g.102877542A>G

CM000674.2:g.102877542A>G

NC\_000012.11:g.103271320A>G

CM000674.1:g.103271320A>G

NC\_000012.10:g.101795450A>G

NG\_008690.1:g.45061T>C

NG\_008690.2:g.85869T>C

ENST00000553106.6:c.361T>C

ENST00000307000.7:c.346T>C

ENST00000549111.5:n.457T>C

ENST00000550978.6:c.345T>C

ENST00000551337.5:c.361T>C

ENST00000551988.5:n.450T>C

ENST00000553106.5:c.361T>C

NM\_000277.1:c.361T>C

NM\_000277.2:c.361T>C

NM\_001354304.1:c.361T>C

NM\_000277.3:c.361T>C

**Pathogenic**

**Met criteria codes** 5

PS3\_Supporting

PP4\_Moderate

PP3\_Strong

PM3

PM2\_Supporting

**Not Met criteria codes** 1

PM5

**Evidence Links** 0

### Expert Panel

Phenylketonuria VCEP [↗](#)

### Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

*Phenylketonuria VCEP*

The NM\_000277.3(PAH):c.361T>C variant in PAH is a missense variant predicted to cause substitution of phenylalanine by leucine at amino acid 121 (p.Phe121Leu). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4\_Moderate, PMIDs: 28754886, 30459323). This variant has been detected in at least 2 individuals with Phenylketonuria. Both were compound heterozygous for the variant and a pathogenic variant (p.Arg241Cys). Parental testing was not reported. (PMIDs: 30459323, 28754886) (PM3). This variant is absent from gnomAD v4.1.0 (PM2\_Supporting). In vitro expression study of this variant in COS-7 cells showed <50% enzyme activity in vitro with < 10 benign/pathogenic variant controls, indicating that this variant impacts protein function (PMID: 24327145; PS3\_Supporting). The computational predictor REVEL gives a score of 0.995, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3\_Strong). In summary, this variant meets criteria to be classified as pathogenic for PAH deficiency. PAH-specific ACMG/AMP criteria applied: PS3\_supporting, PM2\_supporting, PM3, PP3\_strong, PP4\_moderate. Version 2.0, 7/16/2024.

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                  |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PS3_Supporting |    |    | In vitro expression study of novel mutations in phenylalanine hydroxylase gene in COS-7 cells showed <50% enzyme activity in vitro with < 10 benign/pathogenic variant controls indicating that this variant impacts protein function (PMID: 24327145)(PS3_Supporting).                                                          |
| PP4_Moderate   |    |    | At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for Phenylketonuria (PP4_Moderate, PMIDs: 28754886, 30459323). |
| PP3_Strong     |  |  | The computational predictor REVEL gives a score of 0.995, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).                                                                                                                                                          |
| PM3            |  |  | This variant has been detected in 2 individuals with Phenylketonuria. Of those individuals, both were compound heterozygous for the variant and a pathogenic variant (p.Arg241Cys). Parental testing was not reported. (PMIDs: 30459323, 28754886) (PM3)                                                                         |
| PM2_Supporting |  |  | This variant is absent from gnomAD v4.1.0 (PM2_Supporting).                                                                                                                                                                                                                                                                      |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                    |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|
| PM5 |  |  | F121S and F121V are US by PAH VCEP |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|

Curation History 

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