

Variant: *NM\_000277.3(PAH):c.1229T>C (p.Phe410Ser)*

Version: 1.0

CA229405 [↗](#)

102571 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 01797166-5f8d-47c6-91c4-0a5273521d2c

**Approved on:** 2025/8/15

**Published on:** 2025/8/15

### HGVS expressions

**NM\_000277.3(PAH):c.1229T>C (p.Phe410Ser)**

**NM\_000277.3:c.1229T>C**

NC\_000012.12:g.102840486A>G

CM000674.2:g.102840486A>G

NC\_000012.11:g.103234264A>G

CM000674.1:g.103234264A>G

NC\_000012.10:g.101758394A>G

NG\_008690.1:g.82117T>C

NG\_008690.2:g.122925T>C

ENST00000553106.6:c.1229T>C

ENST00000307000.7:c.1214T>C

ENST00000551114.2:n.891T>C

ENST00000553106.5:c.1229T>C

ENST00000635477.1:c.333T>C

ENST00000635528.1:n.744T>C

NM\_000277.1:c.1229T>C

NM\_000277.2:c.1229T>C

NM\_001354304.1:c.1229T>C

NM\_001354304.2:c.1229T>C

**Pathogenic**

**Met criteria codes** **5**

PP4\_Moderate

PP3\_Strong

PM2\_Supporting

PM3

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.1229T>C variant in PAH is a missense variant predicted to cause substitution of phenylalanine to serine at amino acid 410 (p.Phe410Ser). 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:26542770, 10679941). This variant has been detected in 2 individuals with Phenylketonuria. Of those individuals, both were compound heterozygous for the variant and distinct likely pathogenic p.P281L (parental testing was not reported) and pathogenic p.I306V (in trans) variants (PM3; PMID: 26542770). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000008476 in European (non-Finnish) population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2\_Supporting, meeting this criterion (PM2\_Supporting). The computational predictor REVEL gives a score of 0.992, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3\_Strong). Two different missense variants, c.1229T>G (p.Phe410Cys) and c.1229T>G (p.Phe410Cys) are in the same codon have been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2\_supporting, PM3, PP3\_strong, PP4\_moderate, PM5. Version 2.0, 7/16/2024.

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                  |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 (PMIDs:26542770, 10679941). |
| PP3_Strong     |    |    | The computational predictor REVEL gives a score of 0.992, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).                                                                                                                                          |
| PM2_Supporting |  |  | The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000008476 in European (non-Finnish) population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting).                                          |
| PM3            |  |  | This variant has been detected in 2 individuals with Phenylketonuria. Of those individuals, both were compound heterozygous for the variant and distinct likely pathogenic p.P281L (parental testing was not reported) and pathogenic p.I306V (in trans) variants (PMID: 26542770).                              |
| PM5            |  |  | Two different missense variants, c.1229T>G (p.Phe410Cys) and c.1229T>G (p.Phe410Cys) are in the same codon have been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5).                                                                                  |

Curation History 

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