

Variant: *NM\_001354304.2:c.749C>T*

Version: 1.0

CA386295701 [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 918f78dd-ba44-4fd9-9dd6-6417e8d6b430

**Approved on:** 2026/4/15

**Published on:** 2026/4/15

### HGVS expressions

**NM\_001354304.2:c.749C>T**

NC\_000012.12:g.102852908G>A

CM000674.2:g.102852908G>A

NC\_000012.11:g.103246686G>A

CM000674.1:g.103246686G>A

NC\_000012.10:g.101770816G>A

NG\_008690.1:g.69695C>T

NG\_008690.2:g.110503C>T

ENST00000553106.6:c.749C>T

ENST00000307000.7:c.734C>T

ENST00000549247.6:n.508C>T

ENST00000553106.5:c.749C>T

NM\_000277.1:c.749C>T

NM\_000277.2:c.749C>T

NM\_001354304.1:c.749C>T

NM\_000277.3:c.749C>T

**Likely Pathogenic**

**Met criteria codes** **4**

PP3\_Moderate

PP4

PM1

PM2\_Supporting

**Not Met criteria codes** **2**

PS3

PM3

**Evidence Links** **1**

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 c.749C>T variant in PAH is a missense variant predicted to cause substitution of serine by phenylalanine at amino acid 250 (p.Ser250Phe). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L

(2mg/dL), which is highly specific for PAH deficiency (PMID: 28982351). This individual was compound heterozygous for the variant and a variant of uncertain significance confirmed in trans by parental testing (0.25 PM3 points, PM3 does not apply). This variant is absent from gnomAD v4.1.0 (PM2\_Supporting). This variant resides within a region, amino acids 246-266, of PAH that is defined as a critical functional domain by the ClinGen PAH Variant Curation Expert Panel (PM1). The computational predictor REVEL gives a score of 0.938, which is above the threshold of 0.644, evidence that correlates with deleterious impact to PAH function; as PM1 is applied PP3 will be applied at the moderate level as not to exceed strong (PP3\_moderate). In summary, this variant meets the criteria to be classified as Likely pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PM1, PP3\_moderate, PP4, PM2\_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

|                |                                                                                   |                                                                                   |                                                                                                                                                |
|----------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3_Moderate   |  |  | REVEL 0.938                                                                                                                                    |
| PP4            |  |  | Detected in a patient with PAH deficiency (373 μmol/L Phe). Patients with BH4 cofactor deficiency were excluded by BH4 loading. PMID: 28982351 |
| PM1            |  |  | Missense substitution of residues important in cofactor binding of PAH: Ser250                                                                 |
| PM2_Supporting |  |  | Absent from gnomAD v4                                                                                                                          |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PS3 |                                                                                     |  | <p>the levels of mutant PAH proteins decreased significantly compared to the wild type control, in both E. coli and HEK293T cells. The lower expression in mutant groups indicated that PAH protein expression was impaired by variants. Exact numbers or % of wt were not reported.</p> <p>Vectors expressing the corresponding PAH variants were generated for expression in E. coli and in HEK293T cells. The RNA expression of the three PAH variants was measured by RT-qPCR. The mutant PAH protein levels were determined by SDS-PAGE, western blot and ELISA. the levels of mutant PAH proteins decreased significantly compared to the wild type control, in both E. coli and HEK293T cells. The lower expression in mutant groups indicated that PAH protein expression was impaired by variants. In general, all four mutations did not affect the transcription of the PAH gene, however, PAH protein synthesis and/or stability was disturbed. Exact numbers or % of wt were not reported. <a href="#">PubMed:29653233</a> </p> |
| PM3 |  |  | Detected in trans by parental testing with a missense variant of unknown significance p.Arg53His (PMID: 28982351) 0.25 points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Curation History 

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