

Variant: *NM_000277.1:c.1043T>C*

Version: 1.0

CA16020922 [↗](#)

932253 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 75421939-afbe-47f8-b317-d3847d450e4e

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HGVS expressions

NM_000277.1:c.1043T>C

NC_000012.12:g.102844358A>G

CM000674.2:g.102844358A>G

NC_000012.11:g.103238136A>G

CM000674.1:g.103238136A>G

NC_000012.10:g.101762266A>G

NG_008690.1:g.78245T>C

NG_008690.2:g.119053T>C

ENST00000553106.6:c.1043T>C

ENST00000307000.7:c.1028T>C

ENST00000549247.6:n.802T>C

ENST00000551114.2:n.705T>C

ENST00000553106.5:c.1043T>C

ENST00000635477.1:c.147T>C

ENST00000635528.1:n.558T>C

NM_000277.2:c.1043T>C

NM_001354304.1:c.1043T>C

NM_000277.3:c.1043T>C

NM_001354304.2:c.1043T>C

Likely Pathogenic

Met criteria codes **4**

PM2

PM5

PP4_Moderate

PP3

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1043T>C (p.Leu348Pro) variant in PAH has been reported in a Chinese patient with PAH deficiency (BH4 deficiency excluded) (PMID: 23932990) This variant is absent from population databases. A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and

REVEL=0.981. Another missense change at the same amino acid is pathogenic: p.Leu348Val Pathogenic by 7 submitters. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM5, PP3.

Met criteria codes

PM2		Absent from controls in ExAC, gnomAD, 1000 Genomes, ESP
PM5		p.Leu348Val Pathogenic 7 submitters
PP4_Moderate		PMID 23932990: In all patients, hyperphenylalaninemia (HPA) had been detected by either national screening or presence of neurological deterioration at elder age with a plasma phenylalanine (Phe) cut-off level of 120 μmol/L. A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PMID 23932990: 338 unrelated Chinese patients with two presumably causative alterations in the Pah gene from January 2006 through December 2012 were recorded in our database. In all patients, hyperphenylalaninemia (HPA) had been detected by either national screening (57.10%, 193/338) or presence of neurological deterioration at elder age (42.90%, 145/338) with a plasma phenylalanine (Phe) cut-off level of 120 μmol/L. A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. Patients were classified as classic PKU (Phe, more than 1200 μmol/L), moderate PKU (Phe, 900 to 1200 μmol/L), mild PKU (Phe, 600 to 900 μmol/L) and MHP who keeps their Phe levels below 600 μmol/L on a free diet. Appendix A: as unclassified patient. PubMed:23932990
PP3		Predicted deleterious in SIFT, PolyPhen2, MutationTaster. REVEL=0.981

Curation History

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