

Variant: NM_001354304.2:c.441T>C

Version: 1.0

CA481332664 [↗](#)

987766 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 29c30051-bb9c-4220-902f-e83b24b5fdb3

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HGVS expressions

NM_001354304.2:c.441T>C

NC_000012.12:g.102877462A>G

CM000674.2:g.102877462A>G

NC_000012.11:g.103271240A>G

CM000674.1:g.103271240A>G

NC_000012.10:g.101795370A>G

NG_008690.1:g.45141T>C

NG_008690.2:g.85949T>C

ENST00000553106.6:c.441T>C

ENST00000307000.7:c.426T>C

ENST00000549111.5:n.537T>C

ENST00000550978.6:c.425T>C

ENST00000551988.5:n.530T>C

ENST00000553106.5:c.441T>C

NM_000277.1:c.441T>C

NM_000277.2:c.441T>C

NM_001354304.1:c.441T>C

NM_000277.3:c.441T>C

Uncertain Significance

Met criteria codes **2**

PP4

PM2

Not Met criteria codes **3**

PP3

PM3

BP7

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.441T>C (p.Pro147=) PAH variant has been reported in 1 Chinese patient with mild hyperphenylalaninemia (PMID: 30459323) detected with the PAH variant of uncertain significance p.Arg53His. A defect in BH4 metabolism was not excluded. This variant is absent

from population databases. It is a synonymous variant with conflicting predictions by splicing prediction algorithms. In summary, this variant meets criteria to be classified as uncertain significance for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4.

Met criteria codes

PP4			PP4_met: This variant was reported in 1 Chinese patient with mild hyperphenylalaninemia (PMID: 30459323). 30459323, Chen - This variant was reported in 1 Chinese patient with PAH deficiency. Phenylalanine plasma concentrations >120 μmol/L were reported for all subjects. Patients with BH4 cofactor deficiency were excluded, however, the paper did not mention urinary pterin analysis and DHPR activity as methods of exclusion.
PM2			PM2_met: This variant is absent from population databases gnomAD and ExAC.

Not Met criteria codes

PP3			PP3_not met: Splicing prediction algorithms have conflicting predictions (Splice AI: benign (0.01), TraP: probably damaging (0.608), MutationTaster: likely to disturb normal splicing).
PM3			PM3_not met: This variant was detected in trans with the PAH variant of uncertain significance p.Arg53His in one patient with mild hyperphenylalaninemia (MHP)(PMID: 30459323). Parental analysis was not performed to confirm compound heterozygosity. (The genotype was listed in the supplemental section as p.[R53H];[P147P], however, it was listed with the incorrect c., c.441A>G. This c.441A>G was not mentioned in the actual paper.)

PubMed:30459323 

BP7			BP7_not met: Splicing prediction algorithms have conflicting predictions (Splice AI: benign (0.01), TraP: probably damaging (0.608), MutationTaster: likely to disturb normal splicing). The nucleotide is highly conserved.
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Curation History



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