

Variant: *NM_000277.2(PAH):c.440C>T (p.Pro147Leu)*

Version: 1.0

CA229543 [↗](#)

102670 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

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HGVS expressions

NM_000277.2(PAH):c.440C>T (p.Pro147Leu)

NM_000277.2:c.440C>T

NC_000012.12:g.102877463G>A

CM000674.2:g.102877463G>A

NC_000012.11:g.103271241G>A

CM000674.1:g.103271241G>A

NC_000012.10:g.101795371G>A

NG_008690.1:g.45140C>T

NG_008690.2:g.85948C>T

NM_000277.1:c.440C>T

NM_001354304.1:c.440C>T

NM_000277.3:c.440C>T

ENST00000307000.7:c.425C>T

ENST00000549111.5:n.536C>T

ENST00000550978.6:n.424C>T

ENST00000551988.5:n.529C>T

ENST00000553106.5:c.440C>T

Likely Pathogenic

Met criteria codes **4**

PM3_Strong

PP4_Moderate

PP3

PM2

Evidence Links **5**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.440C>T (p.Pro147Leu) variant in PAH has been reported in multiple individuals with mild PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 27121329, 26322415, 16527067, 30050108, 28982351). This variant is absent in population databases (PM2). This variant was detected in trans with known pathogenic variants p.R261Ter (PMID: 27121329); c.611A>G (PMID: 30050108); p.S70del (PMID: 28982351) (PM3_strong). Computational evidence supports a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PP3.

Met criteria codes		
PM3_Strong	 	<p>Detected in trans with p.R261Ter (P, 5 submitters) PMID: 27121329; c.611A>G (P/LP, 4 submitters) PMID: 30050108; p.S70del (P, 3 submitters) PMID: 28982351</p> <hr/> <p>3 patients with p.Pro147Leu in trans with: S70del; p.His170Arg; p.Arg53His. Peripheral blood samples were collected from the patients and parents. Variable sites in patient genes were aligned with the corresponding sites from the respective parents. PubMed:28982351 </p> <p>Patient genotype: p.[Arg261*];[Pro147Leu]. Segregation analysis was done to rule out the presence of large genomic rearrangements. PubMed:27121329 </p> <p>Patient genotype: c.[440C>T];[1215_1219delAATAC], p.[P147L];[I406Sfs*17]. All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing. PubMed:26322415 </p> <p>From supplemental table: patient genotype p.P147L/c.611A>G (p.EX6-96A>G). The validation tests on parents were performed using Sanger sequencing. PubMed:30050108 </p>
PP4_Moderate	 	<p>c.440C>T (p.P147L) identified in 1 patient with mild PKU. BH4 deficiency was excluded. PMID: 26322415</p> <hr/> <p>PubMed:26503515 </p> <p>c.440C>T (p.P147L) identified in 1 patient with mild PKU. All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2 mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415 </p>
PP3	 	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.94)
PM2		Absent from controls in ExAC/gnomAD, 1000 Genomes, or ESP

Curation History 

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