

Variant: *NM_000277.1:c.1244A>T*

Version: 1.0

CA16020979 [↗](#)

1693245 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 42d78ce7-7836-454d-925f-b7b8d391f90e

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HGVS expressions

NM_000277.1:c.1244A>T

NC_000012.12:g.102840471T>A

CM000674.2:g.102840471T>A

NC_000012.11:g.103234249T>A

CM000674.1:g.103234249T>A

NC_000012.10:g.101758379T>A

NG_008690.1:g.82132A>T

NG_008690.2:g.122940A>T

ENST00000553106.6:c.1244A>T

ENST00000307000.7:c.1229A>T

ENST00000551114.2:n.906A>T

ENST00000553106.5:c.1244A>T

ENST00000635477.1:c.348A>T

ENST00000635528.1:n.759A>T

NM_000277.2:c.1244A>T

NM_001354304.1:c.1244A>T

NM_000277.3:c.1244A>T

NM_001354304.2:c.1244A>T

Pathogenic

Met criteria codes **5**

PP3

PP4

PM2

PM5

PM3_Strong

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1244A>T (p.Asp415Val) variant in PAH has been reported in 2 individuals with PKU, detected in trans with pathogenic variants c.1066-11G>A and c.47_48delCT (PMID: 21890392). This variant is absent in population databases. Computational prediction tools and conservation analysis support a deleterious effect. Another missense variant at the same amino acid is interpreted as pathogenic

(p.Asp415Asn) In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP3, PP4.

Met criteria codes

PP3			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster, REVEL=0.954
PP4			<div>D415V was found in 2 PKU patients. BH4 deficiency was assessed: Phenylalanine and pterin concentrations were measured from dried blood spots using tandem mass spectrometry for phenylalanine and HPLC for pterins. All 13 exons of the PAH gene and 7 exons of the QDPR gene (encoding DHPR), plus their exon-intron boundaries were analyzed. PMID: 21890392</div> <div>35 index patients identified with hyperphenylalaninemia. c.1244A>T (p.Asp415Val) was found in Cases 6 and 20. Phenylalanine and pterin concentrations were measured from dried blood spots using a routine tandem mass spectrometry method for phenylalanine and an HPLC method for pterins. All 13 exons of the PAH gene and 7 exons of the QDPR gene (encoding DHPR), plus their exon-intron boundaries were analyzed. PubMed:21890392 </div>
PM2			Absent from ExAC, gnomAD, 1000G, and ESP
PM5			p.Asp415Asn Pathogenic by 9 submitters/PAH VCEP and LP by 2 submitters
PM3_Strong			<div>Detected in trans with pathogenic variants c.1066-11G>A, c.47_48delCT. Mutations were confirmed by carrier analysis of parents and/or siblings. PMID: 21890392</div> <div>D415V was found in trans with c.47_48delCT, p.S16XfsX1 (VarID 102696, Pathogenic/LP) in 1 patient and c.1066 – 11G > A (VarID 607, Pathogenic) in another patient. Mutations were confirmed by carrier analysis of parents and/or siblings. PubMed:21890392 </div>

Curation History

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