

Variant: NM_000277.1:c.224A>T

CA16020751 [↗](#)

619157 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a02baf54-2908-452e-974a-462fb13bcf24

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HGVS expressions

NM_000277.1:c.224A>T

NC_000012.12:g.102894863T>A

CM000674.2:g.102894863T>A

NC_000012.11:g.103288641T>A

CM000674.1:g.103288641T>A

NC_000012.10:g.101812771T>A

NG_008690.1:g.27740A>T

NG_008690.2:g.68548A>T

NM_000277.2:c.224A>T

NM_001354304.1:c.224A>T

NM_000277.3:c.224A>T

ENST00000307000.7:c.209A>T

ENST00000546844.1:c.224A>T

ENST00000548677.2:n.311A>T

ENST00000548928.1:n.146A>T

ENST00000549111.5:n.320A>T

ENST00000550978.6:n.208A>T

ENST00000551337.5:c.224A>T

ENST00000551988.5:n.313A>T

ENST00000553106.5:c.224A>T

Likely Pathogenic

Met criteria codes **3**

PP4_Moderate

PM3

PM2

Not Met criteria codes **2**

PP3

PM5

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.224A>T (p.Asp75Val) variant in PAH is reported in 1 classic PKU patient. BH4 deficiency was excluded. It was detected in trans with a known pathogenic variant, p.R413P. (PMID: 26322415) This variant is absent from ExAC, gnomAD, 1000G, and ESP.Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PP4_Moderate.

Met criteria codes

PP4_Moderate			Detected in 1 classic PKU patient. BH4 deficiency excluded. PMID: 26322415
			We recruited 165 PKU patients (91 males and 74 females) from 21 newborn screening centers in China. All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. D75V was detected on 1 allele in a patient with classic PKU. PubMed:26322415 
PM3			Detected in trans with R413P PMID: 26322415
			Patient genotype: p.[D75V];[R413P] - VarID592, Pathogenic. All mutations identified in patients were confirmed by analyzing parental DNA. PubMed:26322415 
PM2			Absent from ExAC, gnomAD, 1000G, ESP

Not Met criteria codes

PP3			Conflicting interpretations of pathogenicity. SIFT:T,D; Polyphen2:P,B; MutationTaster:D. REVEL=0.705
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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