

Variant: NM_000277.3(PAH):c.1194A>G (p.Lys398=)

CA229376 [↗](#)

102550 (ClinVar) [↗](#)

Gene: PAH (HGNC:5053)

Condition: phenylketonuria (MONDO:0009861)

Inheritance Mode: Autosomal recessive inheritance

UUID: 70f8e388-4b46-4ba3-bfb6-102e901314c8

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HGVS expressions

NM_000277.3:c.1194A>G

NM_000277.3(PAH):c.1194A>G (p.Lys398=)

NM_000277.1:c.1194A>G

NM_000277.2:c.1194A>G

NM_001354304.1:c.1194A>G

NM_001354304.2:c.1194A>G

ENST00000307000.7:c.1179A>G

ENST00000549247.6:n.953A>G

ENST00000551114.2:n.856A>G

ENST00000553106.5:c.1194A>G

ENST00000635477.1:n.298A>G

ENST00000635528.1:n.709A>G

NC_000012.12:g.102843651T>C

CM000674.2:g.102843651T>C

NC_000012.11:g.103237429T>C

CM000674.1:g.103237429T>C

NC_000012.10:g.101761559T>C

NG_008690.1:g.78952A>G

NG_008690.2:g.119760A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PP4_Moderate

PM3_Strong

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1194A>G (p.Lys398Lys) variant in PAH has been reported in 1 in 2 Chinese patients with moderate/classic PKU and BH4 deficiency excluded. (PMIDs: 25894915, 28982351; PP4_Moderate). Both patients were compound heterozygotes with pathogenic variants R413P and R241C confirmed in trans (PM3_Strong). This variant is present at an extremely low frequency with a MAF of 0.00005438 in the gnomAD East Asian population. (PM2). There is consensus of computational predictors that there is potential alteration of splicing via activation of a cryptic splice site near the end of exon 11. In summary, this variant meets criteria to be classified as Likely Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3_Strong, PP3, PP4_Moderate.

Met criteria codes

PP3	✓	HSF (87.18>97.27=>11.57%), MaxEntScan (6.6>10.51=> 59.24%) and SpliceAI (0.82) agree that there is activation of a cryptic splice site near the end of exon 11. Furthermore, the activated cryptic donor site is stronger than the nearby canonical site (HSF 87, MaxEntScan 6) and SpliceAI predicts loss of the canonical donor site (0.5). Overall, there is consensus for potential alteration of splicing which would cause a 5bp deletion and frameshift.
PM2	✓	The variant is present at an extremely low frequency with an overall allele frequency in gnomAD of 0.000003979 and a MAF of 0.00005438 (1/18390 alleles) in the East Asian population.
PP4_Moderate	✓	PMID: 25894915 and PMID: 28982351 - K398K detected in 2 Chinese patients with moderate/classic PKU and BH4 deficiency excluded. <div style="border: 1px solid #ccc; padding: 2px; display: inline-block; margin-bottom: 2px;">PubMed:10394930 ↗</div> <div style="border: 1px solid #ccc; padding: 2px; display: inline-block;">PubMed:25894915 ↗</div>
PM3_Strong	✓	Two compound heterozygotes have been reported (PMID: 28982351 and PMID: 25894915) with pathogenic variants R413P and R241C confirmed in trans. <div style="border: 1px solid #ccc; padding: 2px; display: inline-block;">PubMed:28982351 ↗</div>

Not Met criteria codes

PM5	✗	At same codon as c.1194A>C (p.K398N) curated as VUS by ClinGen PAH VCEP
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Curation History [↗](#)

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
No matching records found							

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