

Variant: *NM_000277.3(PAH):c.1074A>T (p.Leu358Phe)*

Version: 1.0

CA6748747 [↗](#)

556817 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6b077bf4-fd1f-45e4-9b6b-fdad12e855aa

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HGVS expressions

NM_000277.3(PAH):c.1074A>T (p.Leu358Phe)

NM_000277.3:c.1074A>T

NC_000012.12:g.102843771T>A

CM000674.2:g.102843771T>A

NC_000012.11:g.103237549T>A

CM000674.1:g.103237549T>A

NC_000012.10:g.101761679T>A

NG_008690.1:g.78832A>T

NG_008690.2:g.119640A>T

ENST00000553106.6:c.1074A>T

ENST00000307000.7:c.1059A>T

ENST00000549247.6:n.833A>T

ENST00000551114.2:n.736A>T

ENST00000553106.5:c.1074A>T

ENST00000635477.1:c.178A>T

ENST00000635528.1:n.589A>T

NM_000277.1:c.1074A>T

NM_000277.2:c.1074A>T

NM_001354304.1:c.1074A>T

NM_001354304.2:c.1074A>T

Likely Pathogenic

Met criteria codes **4**

PP3

PP4

PM2

PM3

Not Met criteria codes **1**

PS3

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1074A>T (p.Leu358Phe) variant in PAH meets criteria to be classified as likely pathogenic. PAH-specific ACMG/AMP criteria applied: PM2: Variant is present at low frequency in gnomAD (0.0000) and ExAC (0.00002). Absent from 1000 Genomes. PM3: Found to co-occur with F331S in one patient with mild HPA, but no additional studies to demonstrate phase of variants (PMID: 23764561). Found to co-occur with other non-PKU HPA mutation I306V, phase was not confirmed (PMID: 23357515). Found to co-occur in two patients with L348V and R408W with mild and classic PKU, respectively. (PMID: 24350308) PP3: Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster). PP4: In both studies, patients were recruited for their abnormal Phelevels defined as HPA <600umol or 120-600umol. There was no additional testing done to rule out other similar analyte disorders. PS3_Not Met: Functional studies in E. Coli model used and relative specific activity of L358F is 52+-0.7%, which is above our 50% threshold to apply this line of evidence.

Met criteria codes

PP3			Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster)
PP4			In both studies, patients were recruited for their abnormal Phelevels defined as HPA <600umol or 120-600umol). There was no additional testing done to rule out other similar analyte disorders
PM2			Variant is present at low frequency in gnomAD (0.00000) and ExAC (0.00002). Absent from 1000 Genomes
PM3			This variant was reported in combination with another PAH variant F331S (Var ID 371278, LP, 1 submitter) in one patient with mild hyperphenylalaninemia in Polak et al 2013. In Réblová et al 2013 study, found to co-occur with I306V (Variation ID: 618, P/LP, 8 submitters). In Bik-Multonowski et al 2013, found in two different patients. Found in one patient with mild PKU co-occured with L348V (Var ID: 92727, P, 8 submitters). Other patient has classic PKU, co-occured with R408W (Var ID: 577, P, 19 submitters). Phase was not confirmed in any study.

Not Met criteria codes

PS3			This functional study examined the impact of mutated PAH enzymes. It was determined that the L358F variant had 52% residual activity compared to wildtype in a prokaryotic in vitro assay. There was not a significant impact with the addition of chaperones. In the eukaryotic model, the L358F variant produced 17.85% of the wildtype protein expression. There was no change with the addition of sepiaterin, indicating BH4 nonresponsiveness. It is predicted that this is a mild mutation, as there is some remaining function. The threshold to apply PS3 is less than 50% residual activity, so this cannot be applied.
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Curation History

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