

Variant: *NM_000277.3:c.1118C>A*

Version: 1.0

CA16020943 [↗](#)

932260 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: bfe666a9-8374-404a-9e7a-30ffe15d7f01

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HGVS expressions

NM_000277.3:c.1118C>A

NC_000012.12:g.102843727G>T

CM000674.2:g.102843727G>T

NC_000012.11:g.103237505G>T

CM000674.1:g.103237505G>T

NC_000012.10:g.101761635G>T

NG_008690.1:g.78876C>A

NG_008690.2:g.119684C>A

ENST00000553106.6:c.1118C>A

ENST00000307000.7:c.1103C>A

ENST00000549247.6:n.877C>A

ENST00000551114.2:n.780C>A

ENST00000553106.5:c.1118C>A

ENST00000635477.1:c.222C>A

ENST00000635528.1:n.633C>A

NM_000277.1:c.1118C>A

NM_000277.2:c.1118C>A

NM_001354304.1:c.1118C>A

NM_001354304.2:c.1118C>A

Likely Pathogenic

Met criteria codes **4**

PM3_Supporting

PP3

PM2

PP4_Moderate

Not Met criteria codes **1**

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.1118C>A (p.Ala373Asp) variant in PAH is absent from population databases (PM2). A deleterious effect is predicted in SIFT, PolyPhen-2, MutationTaster, and REVEL = 0.958 (PP3). The variant was detected with R158Q, pathogenic in ClinVar, phase unknown (PM3_Supporting). Variant was detected in patient with HPA defined as excessive blood levels (>120 µmol/l) of phenylalanine (BH4 deficiency ruled out; PP4_Moderate; PMID: 23942198). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_Moderate, PP3, PM3_Supporting.

Met criteria codes

PM3_Supporting			PMID:23942198 - A373D detected with R158Q, pathogenic in ClinVar, phase unknown - 0.5 points
PubMed:23942198 			
PP3			Predicted damaging by SIFT, probably damaging by PolyPhen, and disease causing by Mutation Taster. REVEL = 0.958.
PM2			absent from population databases
PP4_Moderate			C10 is part of a cohort of 95 HPA patients with HPA defined as excessive blood levels (>120 µmol/l) of phenylalanine. A defect in BH4 cofactor metabolism was excluded by sequencing GCH1, PTS, and QDPR.

Not Met criteria codes

PM5			Same residue as c.1117G>A (p.Ala373Thr) with no classification provided in ClinVar, but curated by PAH VCEP as likely pathogenic (in progress).
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Curation History

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