

Variant: *NM_000277.3(PAH):c.232G>A (p.Glu78Lys)*

Version: 1.0

CA229495 [↗](#)

102636 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 08a8c7fd-3643-44f7-a6d6-69797b731671

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HGVS expressions

NM_000277.3(PAH):c.232G>A (p.Glu78Lys)

NM_000277.3:c.232G>A

NC_000012.12:g.102894855C>T

CM000674.2:g.102894855C>T

NC_000012.11:g.103288633C>T

CM000674.1:g.103288633C>T

NC_000012.10:g.101812763C>T

NG_008690.1:g.27748G>A

NG_008690.2:g.68556G>A

ENST00000553106.6:c.232G>A

ENST00000307000.7:c.217G>A

ENST00000546844.1:c.232G>A

ENST00000548677.2:n.319G>A

ENST00000548928.1:n.154G>A

ENST00000549111.5:n.328G>A

ENST00000550978.6:c.216G>A

ENST00000551337.5:c.232G>A

ENST00000551988.5:n.321G>A

ENST00000553106.5:c.232G>A

NM_000277.1:c.232G>A

NM_000277.2:c.232G>A

NM_001354304.1:c.232G>A

NM_001354304.2:c.232G>A

Likely Pathogenic

Met criteria codes **4**

PP4

PP3_Moderate

PM3

PM2_Supporting

Not Met criteria codes **1**

PM5

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Phenylketonuria VCEP

The c.232G>A (p.Glu78Lys) variant in PAH has been reported in at least two individuals with plasma Phe levels > 120 umol/L; in one patient, it was observed with c.194T>C (p.Ile65Thr) (classified as pathogenic by PAH VCEP Variation ID: 636) and in the other it was observed with c.1222C>T (p.Arg408Trp) (classified as pathogenic by PAH VCEP Variation ID: 577). Confirmation of phase and exclusion of BH4 deficiency were not specified (PMID: 23430918). c.232G>A has also been described without further information in two additional publications (PMID: 32668217, 32305867). Finally, c.232G>A has been observed in a patient with moderate PKU who also had c.1045T>C (p.Ser349Pro), which is not classified by the PAH VCEP (PMID: 31623983). In-vitro functional studies are unavailable. The Pop Max allele frequency is [8.476e-7] for [ENF] chromosomes by gnomAD v4.1.0, which is lower than the ClinGen PAH threshold (≤ 0.0002) for PM2_Supporting. In-silico predictions suggest this variant is pathogenic (REVEL=0.831). In summary, this variant meets criteria to be classified as Likely Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3, PP4, PM2-supporting, PP3-moderate.

Met criteria codes

PP4			Observed in two patients with PKU with plasma Phe levels >120 umol/L (supplemental table, one with Phe levels ranging from 411-669, the other 1012-1180); exclusion of BH4 deficiency not described (PMID: 23430918).
PP3_Moderate			Damaging in SIFT, Probably Damaging and Possibly Damaging in PP-2, Disease-causing in MutationTaster, REVEL=0.831
PM3			Observed with c.194T>C (p.Ile65Thr) (classified as path by PAH VCEP Variation ID: 636) and c.1222C>T (p.Arg408Trp) (classified as path by PAH VCEP Variation ID: 577) in two patients with PKU with plasma Phe levels >120 umol/L (supplemental table). Phase not confirmed; exclusion of BH4 deficiency not described (PMID: 23430918).
PM2_Supporting			ThePop Max allele frequency is [8.476e-7] for [ENF] chromosomes by gnomAD v4.1.0, which is lower than the ClinGen PAH threshold (≤ 0.0002) for PM2_Supporting, and therefore meets this criterion (PM2_Supporting).

Not Met criteria codes

PM5			c.233A>T (p.Glu78Val) classified as VUS by PAH VCEP (Variation ID: 872831), c.232G>C (p.Glu78Gln) classified as VUS by PAH VCEP (Variation ID: 872830).
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