

Variant: *NM_000277.1(PAH):c.614A>C (p.Glu205Ala)*

Version: 1.0

CA229658 [↗](#)

102760 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d53de39d-1a1d-43ec-8f2d-43210b22f12e

Approved on: 2026/6/17

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HGVS expressions

NM_000277.1(PAH):c.614A>C (p.Glu205Ala)

NM_000277.1:c.614A>C

NC_000012.12:g.102855228T>G

CM000674.2:g.102855228T>G

NC_000012.11:g.103249006T>G

CM000674.1:g.103249006T>G

NC_000012.10:g.101773136T>G

NG_008690.1:g.67375A>C

NG_008690.2:g.108183A>C

ENST00000553106.6:c.614A>C

ENST00000307000.7:c.599A>C

ENST00000549111.5:n.710A>C

ENST00000553106.5:c.614A>C

NM_000277.2:c.614A>C

NM_001354304.1:c.614A>C

NM_000277.3:c.614A>C

NM_001354304.2:c.614A>C

Likely Pathogenic

Met criteria codes **5**

PM3_Supporting

PP4

PM5_Supporting

PP3_Strong

PM2_Supporting

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.614A>C variant in PAH is a missense variant predicted to cause substitution of glutamic acid by alanine at amino acid 205 (p.Glu205Ala). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) without analysis of urine pterins, DHPR activity, or sequencing to exclude defects of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Supporting, PMID: 11180595). This individual was compound heterozygous for the variant and a pathogenic variant (phase unknown, PM3_supporting). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.969, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Another missense variant c.613G>A (p.Glu205Lys) [ClinVar Variation ID: 102759] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP3_strong, PP4, PM2_supporting, PM3_supporting, PM5_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PM3_Supporting			R252W (P 7 submitters); parental analysis not reported PMID: 11180595
PP4			A PKU patient presented the E205A mutation, c.614A>C. The patient had a neonatal diagnosis, with phenylalanine level indicating moderate PKU, and received diet therapy soon after, being currently asymptomatic. PMID: 11180595
PM5_Supporting			p.E205K is likely pathogenic by PAH VCEP
PP3_Strong			REVEL=0.969
PM2_Supporting			Absent from controls in gnomAD v4.1

Curation History

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