

Variant: *NM_000277.1(PAH):c.1054G>T (p.Gly352Cys)*

Version: 1.0

CA229309 [↗](#)

102497 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 8449d96a-9a92-42e8-9402-05c52f91a5eb

Approved on: 2025/11/29

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HGVS expressions

NM_000277.1(PAH):c.1054G>T (p.Gly352Cys)

NM_000277.1:c.1054G>T

NC_000012.12:g.102844347C>A

CM000674.2:g.102844347C>A

NC_000012.11:g.103238125C>A

CM000674.1:g.103238125C>A

NC_000012.10:g.101762255C>A

NG_008690.1:g.78256G>T

NG_008690.2:g.119064G>T

ENST00000553106.6:c.1054G>T

ENST00000307000.7:c.1039G>T

ENST00000549247.6:n.813G>T

ENST00000551114.2:n.716G>T

ENST00000553106.5:c.1054G>T

ENST00000635477.1:c.158G>T

ENST00000635528.1:n.569G>T

NM_000277.2:c.1054G>T

NM_001354304.1:c.1054G>T

NM_000277.3:c.1054G>T

NM_001354304.2:c.1054G>T

Pathogenic

Met criteria codes **5**

PP4_Moderate

PP3_Strong

PM3

PM5_Supporting

PM2_Supporting

Evidence Links **1**

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.1054G>T variant in PAH is a missense variant predicted to cause substitution of glycine by cysteine at amino acid 352 (p.Gly352Cys). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND normal urine pterins and normal DHPR activity excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID 16601866). Of those individuals, one was compound heterozygous for the variant and a pathogenic variant confirmed in trans by parental testing (PM3). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001602 in the remaining population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.994, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Another missense variant c.1054G>C (p.Gly352Arg) [ClinVar Variation ID: 102496] 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 criteria to be classified as pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP4_Moderate, PM2_supporting, PM3, PP3_strong, PM5_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PP4_Moderate			PMID 16601866: Table 1: p.Gly352Cys/IVS10–11G>A in one patient with mPKU (Phe 600–1200 μmol/L). A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PMID 16601866: Table 1: p.Gly352Cys/IVS10–11G>A in one patient with mPKU (Phe 600–1200 μmol/L). A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:16601866
PP3_Strong			The computational predictor REVEL gives a score of 0.994, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM3			PMID 16601866: Table 1: p.Gly352Cys/IVS10–11G>A (P- 7 submitters) All the mutations identified were confirmed by analysing parentalDNA, which also enabled us to follow the segregation of the mutations. PMID 16601866: Table 1: p.Gly352Cys/IVS10–11G>A in one patient with mPKU (Phe 600–1200 μmol/L). PubMed:16601866
PM5_Supporting			Another missense variant c.1054G>C (p.Gly352Arg) [ClinVar Variation ID: 102496] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001602 in the remaining population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting).

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