

Variant: NM_000277.1:c.1037G>A

Version: 1.0

CA16020921 [↗](#)

458078 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ccb4bee2-16a6-4799-8548-6186508934f3

Approved on: 2026/2/18

Published on: 2026/3/1

HGVS expressions

NM_000277.1:c.1037G>A

NC_000012.12:g.102844364C>T

CM000674.2:g.102844364C>T

NC_000012.11:g.103238142C>T

CM000674.1:g.103238142C>T

NC_000012.10:g.101762272C>T

NG_008690.1:g.78239G>A

NG_008690.2:g.119047G>A

ENST00000553106.6:c.1037G>A

ENST00000307000.7:c.1022G>A

ENST00000549247.6:n.796G>A

ENST00000551114.2:n.699G>A

ENST00000553106.5:c.1037G>A

ENST00000635477.1:c.141G>A

ENST00000635528.1:n.552G>A

NM_000277.2:c.1037G>A

NM_001354304.1:c.1037G>A

NM_000277.3:c.1037G>A

NM_001354304.2:c.1037G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate

PP3_Strong

PM3

PM2_Supporting

Not Met criteria codes 2

PM1

PM5

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.1037G>A variant in PAH is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid 346 (p.Gly346Glu). 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 19394257). Of reported individuals, one was compound heterozygous for the variant and a pathogenic variant (unknown phase), and one individual was homozygous for the variant (1 point, PMID: 32668217, PM3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.979, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Two missense variants, c.1036G>A (p.Gly346Arg) and c.1036G>C (p.Gly346Arg) [ClinVar Variation ID 102485, 102486], in the same codon have been classified as Likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel. However, the PAH VCEP is not applying PM5 as evidence since the p.Gly346Glu variant is also classified as Likely pathogenic. 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_moderate, PM3, PM2_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PP4_Moderate			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 19394257). BH4 deficiency was excluded in all patients by measuring urinary pterins and dried blood dihydropteridine reductase activity.
PP3_Strong			The computational predictor REVEL gives a score of 0.979, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM3			This variant has been detected in at least two individuals with Phenylketonuria. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (unknown phase), and one individual was homozygous for the variant (1 point, PMID: 32668217, PM3). genotype not reported in PMID: 19394257.
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM1			Missense substitution of residues important in the active site architecture and/or substrate and/or cofactor binding of PAH: Gly346. Not applying since PP3 strong applies
PM5			Two missense variants, c.1036G>A (p.Gly346Arg) and c.1036G>C (p.Gly346Arg) [ClinVar Variation ID 102485, 102486], in the same codon have been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel [PM5]. Not applying to keep at LP, similar to other missense variants at this aa per PAH VCEP 2/18/26.

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Showing 1 to 1 of 1 rows

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