

Variant: *NM_000277.2(PAH):c.386A>G (p.Asp129Gly)*

Version: 1.0

CA229527 [↗](#)

102661 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1c39ee9a-5884-4352-9d86-335d9e4491cb

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HGVS expressions

NM_000277.2(PAH):c.386A>G (p.Asp129Gly)

NM_000277.2:c.386A>G

NC_000012.12:g.102877517T>C

CM000674.2:g.102877517T>C

NC_000012.11:g.103271295T>C

CM000674.1:g.103271295T>C

NC_000012.10:g.101795425T>C

NG_008690.1:g.45086A>G

NG_008690.2:g.85894A>G

NM_000277.1:c.386A>G

NM_001354304.1:c.386A>G

NM_000277.3:c.386A>G

ENST00000307000.7:c.371A>G

ENST00000549111.5:n.482A>G

ENST00000550978.6:n.370A>G

ENST00000551337.5:c.386A>G

ENST00000551988.5:n.475A>G

ENST00000553106.5:c.386A>G

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM2

PM3

Evidence Links **5**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.386A>G (p.Asp129Gly) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 8981952). This variant has extremely low frequency in gnomAD (MAF: 0.00001; PM2). This variant was detected in trans with known pathogenic variant c.1066-11G>A (PM3; PMID: 27121329). Computational evidence supports a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP4_Moderate			Detected on 2 alleles in Spanish PKU patients, BH4 defects excluded. PMID: 8981952
			Patients were considered as having PKU when the serum phenylalanine levels at diagnosis were >600 umol/liter and after exclusion of a defect in tetrahydrobiopterine metabolism. D129G detected on 2 alleles. PubMed:8981952
PP3			Deleterious effect predicted: SIFT, Polyphen2, MutationTaster, REVEL=0.984
PM2			Extremely low frequency (highest MAF in ENF gnomAD: 0.00001
PM3			Detected in trans with c.1066-11G>A PMID:27121329
			Patient 5 genotype: p.D129G / p.R408W. Parental segregation not reported/performed. PubMed:23062575
			Patient genotype: c.194T>C;c.386A>G / p.(Ile65Thr);p.(Asp129Gly). Parental segregation not reported/performed. PubMed:26666653
			detected in the homozygous state. Parental segregation not reported/performed. PubMed:23357515
			2 patients reported: 1 homozygous; patient 2: c.1066-11G4A; p.Asp129Gly. Segregation analysis was done to rule out the presence of large genomic rearrangements. PubMed:27121329

Curation History

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Showing 1 to 1 of 1 rows

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