

Variant: *NM_000277.1(PAH):c.649T>G (p.Cys217Gly)*

Version: 1.0

CA229673 [↗](#)

102771 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: de77af67-a3ab-40f2-b946-61129a7d7e8f

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HGVS expressions

NM_000277.1:c.649T>G

NM_000277.1(PAH):c.649T>G (p.Cys217Gly)

NC_000012.12:g.102855193A>C

CM000674.2:g.102855193A>C

NC_000012.11:g.103248971A>C

CM000674.1:g.103248971A>C

NC_000012.10:g.101773101A>C

NG_008690.1:g.67410T>G

NG_008690.2:g.108218T>G

ENST00000553106.6:c.649T>G

ENST00000307000.7:c.634T>G

ENST00000549111.5:n.745T>G

ENST00000553106.5:c.649T>G

NM_000277.2:c.649T>G

NM_001354304.1:c.649T>G

NM_000277.3:c.649T>G

NM_001354304.2:c.649T>G

Likely Pathogenic

Met criteria codes **3**

PM2

PP4_Moderate

PM3_Strong

Not Met criteria codes **2**

PM5

PP3

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.649T>G (p.Cys217Gly) variant in PAH has been reported in 3 individuals with PAH deficiency (BH4 deficiency excluded). This variant is absent in population databases. This variant was detected with pathogenic variants: p.P281L (PMID: 8807319), IVS10-11G>A, and p.V245A (PMID: 27121329). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong.

Met criteria codes

PM2		Not found in ExAC, gnomAD, 1000G or ESP
PP4_Moderate		<p>C217G found in 3 patients with PKU/mild PKU. Other causes of HPA were ruled out in 2 patients. PMID: 27121329, PMID: 23514811, PMID: 8807319</p> <hr/> <p>179 patients (78 male and 91 female) of the Andalusian community whose cut-off value for phenylalanine is 180 mM. C217G found in 2 patients. 1 patient had Mild PKU (Phe between 300–600mM, tolerance 600–800mg per day). PubMed:23514811 </p> <p>34 PKU patients in the Netherlands. Classified as PKU when serum Phe was > 600 umol/l before treatment and when other causes of HPA had been ruled out. Proband 10: C217G;P281L, PKU phenotype. PubMed:8807319 </p>
PM3_Strong		<p>C217G in trans with P281L (parental analysis not reported, PMID: 8807319), IVS10-11G>A, and V245A (Segregation analysis was done, PMID: 27121329) which are pathogenic in ClinVar</p> <hr/> <p>C217G found in trans with IVS10-11g>a in patient with mild PKU. (VarID 607, Pathogenic in ClinVar) PubMed:23514811 </p> <p>C217G in trans with P281L in PKU patient. P281L is classified as pathogenic ClinVar (VarID 589) PubMed:8807319 </p>

Not Met criteria codes

PM5		C217Y (VarID 102772) and C217R (VarID 102770) clinical significance not provided in ClinVar
PP3		Conflicting predictions: tolerated in SIFT, deleterious in Polyphen and MutationTaster

Curation History

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