The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1:c.1285C>A

CA6748701

551555 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7531cb9b-9ac5-43c2-b83a-24078467de09
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HGVS expressions

NM_000277.1:c.1285C>A
NC_000012.12:g.102840430G>T
CM000674.2:g.102840430G>T
NC_000012.11:g.103234208G>T
CM000674.1:g.103234208G>T
NC_000012.10:g.101758338G>T
NG_008690.1:g.82173C>A
NG_008690.2:g.122981C>A
NM_000277.2:c.1285C>A
NM_001354304.1:c.1285C>A
NM_000277.3:c.1285C>A
ENST00000307000.7:c.1270C>A
ENST00000551114.2:n.947C>A
ENST00000553106.5:c.1285C>A
ENST00000635477.1:n.389C>A
ENST00000635528.1:n.800C>A

Likely Pathogenic

Met criteria codes 3

PM2 PM3 PP4_Moderate

Not Met criteria codes 1

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.1285C>A (p.Gln429Lys) variant in PAH is reported in a patient with mild PKU (Phe level 720). BH4 cofactor deficiency was excluded. It was detected with a known pathogenic variant, EX6-96A>G (VarID 590). (PMID: 26503515, 28982351) This variant has a low frequency in gnomAD and ExAC (MAF=0.00002), and absent in 1000G. Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_Moderate, PM3.

Met criteria codes

PM2	✔	Low AF: gnomAD: MAF=0.00002, ExAC 1/121324, 1000G absent.
PM3	✔	Detected with EX6-96A>G (VarID 590; P/LP). Patient 328 has genotype EX6-96A>G (VarID 590; P/LP)/p.Gln429Lys. Peripheral blood samples were collected from the patients and parents in each of the 643 core families. PubMed:28982351
PP4_Moderate	✔	Seen in a patient with mild PKU (Phe level 720). BH4 cofactor deficiency was excluded. PMID: 26503515, 28982351 Patients with BH4 cofactor deficiency were excluded. Patient 328 has mPKU (Phe level 720) and genotype EX6-96A>G/p.Gln429Lys PubMed:28982351 Seen in a patient with PKU identified by newborn screening. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515

Not Met criteria codes

PP3	✖	Predicted tolerated/ benign by SIFT and Polyphen. Predicted deleterious by MutTaster

Curation History

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