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_000277.2(PAH):c.812A>G (p.His271Arg)

CA286508

102850 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d192c79d-a8eb-4120-9330-b886bf5f592a
Approved on: 2018-12-10
Published on: 2018-12-10

HGVS expressions

NM_000277.2:c.812A>G
NM_000277.2(PAH):c.812A>G (p.His271Arg)
NC_000012.12:g.102852845T>C
CM000674.2:g.102852845T>C
NC_000012.11:g.103246623T>C
CM000674.1:g.103246623T>C
NC_000012.10:g.101770753T>C
NG_008690.1:g.69758A>G
NG_008690.2:g.110566A>G
NM_000277.1:c.812A>G
NM_001354304.1:c.812A>G
NM_000277.3:c.812A>G
ENST00000307000.7:c.797A>G
ENST00000549247.6:n.571A>G
ENST00000553106.5:c.812A>G

Likely Pathogenic

Met criteria codes 4

PM2 PM3 PP4_Moderate PP3

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.812A>G (p.His271Arg) variant in the PAH gene has been reported in PKU patients in Henan, and France. Dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading were collected for the Chinese patient. (PMID: 21462123, 26666653, 26503515). This variant was detected with R408W (PMID: 26666653). A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and REVEL=0.969. It has an extremely low frequency in ExAC and gnomAD (MAF=0.00006). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PP4_Moderate, PP3.

Met criteria codes

PM2	✔	Extremely low frequency in ExAC and gnomAD (MAF=0.00006)
PM3	✔	Detected with R408W, PMID: 26666653 Patient genotype: [His271Arg]; [Arg408Trp]. PubMed:26666653
PP4_Moderate	✔	H271R was detected in PKU patients in Henan, and a classic PKU patient in France. dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected for the Chinese patient. PMID: 21462123, 26666653, 26503515 Patients with phenylketonuria (PKU) in Henan province. H271R was detected. PubMed:21462123 p.H21R was detected on 1 allele from Northern China. Plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515 A total of 364 hyperphenylalaninemic patients, including 42 siblings, were investigated. They represented mixed origin people from 20 French Centers for Inborn Errors of Metabolism. According to their blood Phenylalanine concentration at time of diagnosis, these patients were assigned to one of the three phenotype categories. His271Arg was detected in 1 patient with classic PKU (Phe > 1200 µmol/L). PubMed:26666653
PP3	✔	Deleterious effect predicted in SIFT, polyphen2, MutationTaster. REVEL=0.969

Not Met criteria codes

PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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