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Variant: NM_000277.1(PAH):c.1097C>A (p.Pro366His)

Version: 1.0

CA229341

102521 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6adfe34f-36c9-4d33-b7e9-1fb4efef4726
Approved on: 2020/8/14
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HGVS expressions

NM_000277.1(PAH):c.1097C>A (p.Pro366His)
NM_000277.1:c.1097C>A
NC_000012.12:g.102843748G>T
CM000674.2:g.102843748G>T
NC_000012.11:g.103237526G>T
CM000674.1:g.103237526G>T
NC_000012.10:g.101761656G>T
NG_008690.1:g.78855C>A
NG_008690.2:g.119663C>A
ENST00000553106.6:c.1097C>A
ENST00000307000.7:c.1082C>A
ENST00000549247.6:n.856C>A
ENST00000551114.2:n.759C>A
ENST00000553106.5:c.1097C>A
ENST00000635477.1:c.201C>A
ENST00000635528.1:n.612C>A
NM_000277.2:c.1097C>A
NM_001354304.1:c.1097C>A
NM_000277.3:c.1097C>A
NM_001354304.2:c.1097C>A

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PP4_Moderate PM3_Strong

Not Met criteria codes 1

PM5

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1097C>A (p.Pro366His) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 8268925). This variant is absent in population databases. This variant was detected with multiple pathogenic variants: p.R158Q (PMID: 8830172); c.165delT (p.F55fs, PMID: 19292873); c.1066-11G>A (PMID: 22841515); p.P281L (PMID: 21147011). Computational evidence support a deleterious effect. 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, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.929
PM2	✔	Absent from controls in ExAC, gnomAD, 1000G, ESP
PP4_Moderate	✔	P366H seen on 1 PKU allele. Other potential causes of hyperphenylalaninemia had been ruled out (normal serum tyrosine, normal urinary excresion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia). PMID: 8268925 In this study, we conducted a systematic analysis of 53 patients from the Sicilian population. All patients were presenting with blood phenylalanine levels persistently above 150 /umol/L, and diagnosis of PAH deficiency was made when other potential causes of hyperphenylalaninemia had been ruled out. The criteria for inclusion were: normal serum tyrosine, normal urinary excresion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. P366H seen on 1 chromosome. PubMed:8268925
PM3_Strong	✔	Seen in 3 PKU patients with known pathogenic mutations: R158Q (parental testing not reported, PMID: 8830172; c.165delT (p.F55fs). Parental analysis not reported PMID: 19292873; c.1066-11G>A parental analysis not reported; PMID: 22841515; P281L parental analysis not reported PMID: 21147011 Patient F50: R158Q (VarID 587, Pathogenic) /P366H, pre-treatment Phe level 720 umol/L PubMed:8830172 Patient 106: c.1066-11 G>A (VarID 607, Pathogenic) /p.P366H. PubMed:22841515 Seen in trans with P281L (VarID 589, Pathogenic) PubMed:21147011

Not Met criteria codes

PM5	✖	This variant is the only variant found in this codon in ClinVar.

Curation History

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