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Variant: NM_000277.2(PAH):c.974A>G (p.Tyr325Cys)

Version: 1.0

CA220593

92756 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: beb6cce3-600e-4524-83f3-c01b699bc962
Approved on: 2020/2/23
Published on: 2020/2/23

HGVS expressions

NM_000277.2(PAH):c.974A>G (p.Tyr325Cys)
NM_000277.2:c.974A>G
NC_000012.12:g.102844427T>C
CM000674.2:g.102844427T>C
NC_000012.11:g.103238205T>C
CM000674.1:g.103238205T>C
NC_000012.10:g.101762335T>C
NG_008690.1:g.78176A>G
NG_008690.2:g.118984A>G
ENST00000553106.6:c.974A>G
ENST00000307000.7:c.959A>G
ENST00000549247.6:n.733A>G
ENST00000551114.2:n.636A>G
ENST00000553106.5:c.974A>G
ENST00000635477.1:c.78A>G
ENST00000635528.1:n.489A>G
NM_000277.1:c.974A>G
NM_001354304.1:c.974A>G
NM_000277.3:c.974A>G
NM_001354304.2:c.974A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PM2 PP4_Moderate

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.974A>G (p.Tyr325Cys) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded). It was detected with pathogenic/LP variants p.L194P (LP) PMID: 23430918 L348V (P) PMID: 10679941 p.P281L (LP) PMID: 22526846 p.R408W (P) with

parental analysis not reported for 1.5 points. This variant has extremely low frequency in gnomAD (MAF=0.00001). Computational evidence supports a 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, PP3.

Met criteria codes

PP3	✔	In silico analysis supports deleterious effect. REVEL 0.992
PM3	✔	identified with p.L194P (LP) PMID: 23430918 L348V (P 7 submitters) PMID: 10679941 p.P281L (LP) parental analysis not reported PMID: 22526846 p.R408W (P 14 submitters) PubMed:24350308
PM2	✔	Absent from ExAC, MAF=0.00001 in gnomAD.
PP4_Moderate	✔	Single patient with Phe 480umol/L at dx. BH4 defect excluded with urine pterins and DHPR activity. PubMed:10679941 PubMed:22526846 PubMed:23430918

Curation History

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