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Variant: NM_000277.3:c.1174T>A

Version: 1.0

CA6748732

853581 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: b0f1905b-b918-4f3d-95b4-0ffeb33d2386
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HGVS expressions

NM_000277.3:c.1174T>A
NC_000012.12:g.102843671A>T
CM000674.2:g.102843671A>T
NC_000012.11:g.103237449A>T
CM000674.1:g.103237449A>T
NC_000012.10:g.101761579A>T
NG_008690.1:g.78932T>A
NG_008690.2:g.119740T>A
ENST00000553106.6:c.1174T>A
ENST00000307000.7:c.1159T>A
ENST00000549247.6:n.933T>A
ENST00000551114.2:n.836T>A
ENST00000553106.5:c.1174T>A
ENST00000635477.1:c.278T>A
ENST00000635528.1:n.689T>A
NM_000277.1:c.1174T>A
NM_000277.2:c.1174T>A
NM_001354304.1:c.1174T>A
NM_001354304.2:c.1174T>A

Pathogenic

Met criteria codes 3

PP3 PM3_Very Strong PP4_Moderate

Not Met criteria codes 1

PM2

Evidence Links 8

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1174T>A (p.F392I) variant was documented 19 times in patients with PAH deficiency; DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia (PMID: 26503515, 30459323, 26322415, 30747360). This variant was detected in at least 8 mild hyperphenylalaninemia (MHP) patients and 1 classical PKU patient with a pathogenic variant in trans (PMID: 24401910, 29316886, 30050108, 31445982). This missense variant is predicted to be damaging (SIFT), probably damaging (PolyPhen2), and disease causing (MutationTaster). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP3, PP4_moderate, PM3_very strong.

Met criteria codes

PP3	✔	Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster)
PM3_Very Strong	✔	This variant was detected in at least 8 mild hyperphenylalaninemia (MHP) patients and 1 classical PKU patient with a pathogenic variant in trans (PMID: 24401910, 29316886, 30050108, 31445982). This variant was detected in trans with the pathogenic PAH variant Arg408Gln in 1 patient with mild hyperphenylalaninemia. Parental analysis was not performed to confirm compound heterozygosity. This variant was documented in a 2nd patient diagnosed with mild hyperphenylalaninemia (MHP), however, the variant in trans was not specified. PubMed:24401910 This variant was documented in one patient with mild hyperphenylalaninemia with the pathogenic variant c.331C>T (p.Arg111Ter) in trans. Parental analysis was not performed to confirm compound heterozygosity. PubMed:31445982 This variant was documented in 7 Chinese patients diagnosed with mild hyperphenylalaninemia. The reported variant in trans for each of the patients was the pathogenic variant c.1197A>T (in 2 patients), the pathogenic variant c.728G>A (p.Arg243Gln) (in 1 patient), the pathogenic variant c.721C>T (in 1 patient), the VUS c.1099C>G (in 1 patient), c.763T>G (in 1 patient), and c.460T>C (in 1 patient). Parental analysis was performed to confirm compound heterozygosity. PubMed:30050108 This variant was detected in trans with the pathogenic variant p.Tyr356* in 2 patients, one was diagnosed with mild hyperphenylalaninemia and the 2nd was diagnosed with classic PKU. This variant was detected in trans with the pathogenic variant p.Arg243Gln in a patient diagnosed with mild hyperphenylalaninemia. This variant was detected in trans with the pathogenic variant p.Ser70del in a patient diagnosed with mild hyperphenylalaninemia. This variant was detected in a second patient diagnosed with classical PKU, however the variant in trans was not reported. Parental analysis was performed to confirm compound heterozygosity. PubMed:29316886
PP4_Moderate	✔	This variant was documented 19 times in patients with PAH deficiency (PMID: 26503515, 30459323, 26322415, 30747360). This variant was documented three times in Southern Chinese patients and three times in Northern Chinese patients with PAH deficiency (PMID: 26503515). It was not specified whether patient genotypes were homozygous or compound heterozygous for the variant. Subjects in this study were diagnosed through neonatal screening program or by clinical presentation. Phenylalanine plasma concentrations >120 µmol/L were reported for all subjects. Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis, and DHPR activity assay. PubMed:26503515 This variant was documented 5 times in patients diagnosed with mild hyperphenylalaninemia (MHP) in Northwest China. It was not specified whether patient genotypes were homozygous or compound heterozygous for the variant. PubMed:30747360 This variant was documented 7 times in mild hyperphenylalaninemia (Phe value of <360 µmol/L) patients from Zhejiang Province. It was not specified whether patient genotypes were homozygous or compound heterozygous for the variant. PubMed:30459323 This variant was documented in trans with the VUS p.L367V in 1 patient diagnosed with mild hyperphenylalaninemia. PubMed:26322415

Not Met criteria codes

PM2	✖	Present in East Asian populations at frequency of 0.00198 and in all populations at frequency of 0.00040 (1000 Genomes). The PM2 threshold set by the PAH Variant Curation Expert Panel (VCEP) is 0.0002.

Curation History

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