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Variant: NM_000277.2(PAH):c.521T>C (p.Ile174Thr)

Version: 1.0

CA229604

102721 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e09d3bdc-fa6e-47db-a864-8f62a9e00ee7
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HGVS expressions

NM_000277.2(PAH):c.521T>C (p.Ile174Thr)
NM_000277.2:c.521T>C
NC_000012.12:g.102855321A>G
CM000674.2:g.102855321A>G
NC_000012.11:g.103249099A>G
CM000674.1:g.103249099A>G
NC_000012.10:g.101773229A>G
NG_008690.1:g.67282T>C
NG_008690.2:g.108090T>C
NM_000277.1:c.521T>C
NM_001354304.1:c.521T>C
NM_000277.3:c.521T>C
ENST00000307000.7:c.506T>C
ENST00000549111.5:n.617T>C
ENST00000551988.5:n.542T>C
ENST00000553106.5:c.521T>C

Pathogenic

Met criteria codes 5

PM2 PM3 PP4_Moderate PS3 PP3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.521T>C (p.Ile174Thr) variant in PAH has been reported in 2 individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 9634518). This variant is absent from ExAC/gnomAD, 1000 Genomes, ESP (PM2). This variant has 1-15% enzyme activity (PS3; PMID: 11161839). This variant was detected in with p.F299C (P/LP, 6 submitters) (PM3; PMID: 23842451). Computational prediction tools and conservation analysis suggest that the variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PS3, PM2, PM3, PP3

Met criteria codes

PM2	✔	Absent from ExAC/gnomAD, 1000 Genomes, ESP
PM3	✔	detected with p.F299C (P/LP, 6 submitters) 23842451 patient genotype: p.I174T/p.F299C (P/LP, 6 submitters) PubMed:23842451
PP4_Moderate	✔	I174T detected in 2 patients. BH4 deficiency was excluded. PMID: 9634518 I174T detected in 2 patients. In all patients, hyperphenylalaninemia had been detected by national mass screening programs, and PAH deficiency had been assessed after exclusion of a defect in tetrahydrobiopterin metabolism. PubMed:9634518
PS3	✔	PAH enzyme activity in two heterologous in vitro expression systems was 1-15% for the I174T mutant. PMID: 11161839 PAH enzyme activity in pcDNA3/IVT: 10%;15% and pET/E. coli: 1.0% +/- 0.7. The data for the bacterial expression represent three independent experiments. PubMed:11161839
PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.971)

Curation History

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