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Variant: NM_000277.3(PAH):c.1262T>C (p.Ile421Thr)

Version: 1.0

CA229420

102582 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dc8e169b-a5b9-4632-a7b0-9f09dcde0310
Approved on: 2021/5/29
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HGVS expressions

NM_000277.3:c.1262T>C
NM_000277.3(PAH):c.1262T>C (p.Ile421Thr)
NC_000012.12:g.102840453A>G
CM000674.2:g.102840453A>G
NC_000012.11:g.103234231A>G
CM000674.1:g.103234231A>G
NC_000012.10:g.101758361A>G
NG_008690.1:g.82150T>C
NG_008690.2:g.122958T>C
ENST00000553106.6:c.1262T>C
ENST00000307000.7:c.1247T>C
ENST00000551114.2:n.924T>C
ENST00000553106.5:c.1262T>C
ENST00000635477.1:c.366T>C
ENST00000635528.1:n.777T>C
NM_000277.1:c.1262T>C
NM_000277.2:c.1262T>C
NM_001354304.1:c.1262T>C
NM_001354304.2:c.1262T>C

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3_Strong PM2 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.1262T>C (p.Ile421Thr) variant in PAH has been reported in multiple individuals with mild and classic PKU (BH4 deficiency excluded) (PMID: 26503515, PMID: 27121329, PMID: 23514811). This variant has low frequency (MAF=0.00001) in gnomAD. This variant was detected with pathogenic variants: R241H (PMID: 27121329); p.Arg408Gln (PMID: 25456745); IVS5-1G□A, p.Val399= (PMID: 29316886); Ex9_11del (LP PAH VCEP) PMID: 31623983. Computational evidence supports 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_vstrong, PP3.

Met criteria codes

PP4_Moderate	✔	Seen in patients with mild and classic PKU. BH4 cofactor deficiency ruled out. PMID: 26503515, PMID: 27121329, PMID: 23514811 Seen in a patient with Mild PKU-NT (<360 µmol l − 1). In trans with Arg241His. BH4 deficiency ruled out. PubMed:27121329 Seen in a patient with PKU. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515 Seen in a Andalusian patient with PKU. Identified in prenatal screening, BH4 deficiency ruled out. PubMed:23514811
PM3_Strong	✔	Seen in trans with R241H, pathogenic in ClinVar 102804 PMID: 27121329; p.Arg408Gln (P 6 submitters), parental analysis not performed PMID: 25456745; in trans with IVS5-1G□A (P PAH VCEP), p.Val399= (P 5 submitters) PMID: 29316886 Ex9_11del parental analysis not reported (LP PAH VCEP) PMID: 31623983 3.75 pts Seen in a patient with mild PKU in trans with R241H, pathogenic in ClinVar 102804 PubMed:27121329
PM2	✔	Low AF. MAF=0.00001 in gnomAD, absent in 1000G
PP3	✔	Multiple lines of evidence support a deleterious effect. Possibly damaging by Polyphen. Damaging by SIFT and MutTaster.

Not Met criteria codes

PM5	✖	I421S US in ClinVar, curated as LP by PAH VCEP

Curation History

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