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Variant: NM_000277.2(PAH):c.1217T>C (p.Ile406Thr)

CA229398

102567 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 47b1110a-e06d-487d-b096-69829820e761
Approved on: 2018-12-09
Published on: 2018-12-10

HGVS expressions

NM_000277.2(PAH):c.1217T>C (p.Ile406Thr)
NM_000277.2:c.1217T>C
NC_000012.12:g.102840498A>G
CM000674.2:g.102840498A>G
NC_000012.11:g.103234276A>G
CM000674.1:g.103234276A>G
NC_000012.10:g.101758406A>G
NG_008690.1:g.82105T>C
NG_008690.2:g.122913T>C
NM_000277.1:c.1217T>C
NM_001354304.1:c.1217T>C
NM_000277.3:c.1217T>C
ENST00000307000.7:c.1202T>C
ENST00000551114.2:n.879T>C
ENST00000553106.5:c.1217T>C
ENST00000635477.1:n.321T>C
ENST00000635528.1:n.732T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PP4_Moderate PM3_Strong

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1217T>C (p.Ile406Thr) variant in PAH is reported in 2 unrelated patients with PKU; BH4 cofactor deficiency was ruled out. (PMID: 10234516, 27121329, 28754886) This variant was reported in trans with known pathogenic variants p.I65T (PMID: 10234516) and IVS4-1G>A (PMID: 28754886). It is absent in population databases, and multiple lines of 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: PM3_strong, PM2, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	Predicted deleterious/ damaging by multiple lines of evidence.
PM2	✔	Absent from controls
PP4_Moderate	✔	Seen in a patient with mild PKU, BH4 cofactor deficiency ruled out. PMID: 10234516, 27121329 ame patient as other article, but says that cofactor is ruled out and change is located in the catalytic domain. PubMed:27121329 Seen in a patient with mild PKU, defined as a tolerance of 500-900 mg of Phe daily. PubMed:10234516
PM3_Strong	✔	Seen in trans with I65T (PMID: 10234516) and IVS4-1G>A (PMID: 28754886). Patient M1770: p.[IVS4-1G > A] (VarID 102671, P/LP); [Ile406Thr]. PubMed:28754886 Seen in trans with I65T (VarID 636, pathogenic) in a patient with mild PKU. PubMed:10234516

Curation History

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