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Variant: NM_000277.3:c.1115C>G

Version: 1.0

CA16020942

1327554 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 109a434d-9d5c-49f8-9e98-7216865f07d6
Approved on: 2020/8/10
Published on: 2021/9/26

HGVS expressions

NM_000277.3:c.1115C>G
NC_000012.12:g.102843730G>C
CM000674.2:g.102843730G>C
NC_000012.11:g.103237508G>C
CM000674.1:g.103237508G>C
NC_000012.10:g.101761638G>C
NG_008690.1:g.78873C>G
NG_008690.2:g.119681C>G
ENST00000553106.6:c.1115C>G
ENST00000307000.7:c.1100C>G
ENST00000549247.6:n.874C>G
ENST00000551114.2:n.777C>G
ENST00000553106.5:c.1115C>G
ENST00000635477.1:c.219C>G
ENST00000635528.1:n.630C>G
NM_000277.1:c.1115C>G
NM_000277.2:c.1115C>G
NM_001354304.1:c.1115C>G
NM_001354304.2:c.1115C>G

Likely Pathogenic

Met criteria codes 4

PM2 PP4_Moderate PP3 PM3_Strong

Not Met criteria codes 1

PM5

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1115C>G (p.Thr372Arg) variant in PAH has been reported in 3 individuals with classic PKU (BH4 deficiency excluded, PMID: 26503515) detected in trans with pathogenic variants: p.R176* (2 patients) and p.R408W (PMID: 30050108). This variant is absent in population databases. 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: PP4_Moderate, PM2, PM3_strong, PP3.

Met criteria codes

PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PP4_Moderate	✔	T372R was found in 3 patients with classic PKU. BH4 deficiency was assessed by dihydropteridine reductase activity, urinary biopterin and neopterin ratio PMID: 26503515, PMID: 30050108 PAH mutations complied from 796 PKU patients from mainland China. Demographic data and biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected.T372R was found on 2 alleles. PubMed:26503515
PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster. REVEL=0.922
PM3_Strong	✔	Detected in trans with p.R176* (2 patients, P 9 submitters), and p.R408W (P 17 submitters). The validation tests on parents were performed using Sanger sequencing. PMID: 30050108

Not Met criteria codes

PM5	✖	T372S is Likely Pathogenic 2 submitters

Curation History

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