The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.1114A>T (p.Thr372Ser)

Version: 1.0

CA229350

102528 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d7e037fb-45b7-488f-98bc-920b7c13f9eb
Approved on: 2020-08-14
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HGVS expressions

NM_000277.1:c.1114A>T
NM_000277.1(PAH):c.1114A>T (p.Thr372Ser)
NC_000012.12:g.102843731T>A
CM000674.2:g.102843731T>A
NC_000012.11:g.103237509T>A
CM000674.1:g.103237509T>A
NC_000012.10:g.101761639T>A
NG_008690.1:g.78872A>T
NG_008690.2:g.119680A>T
ENST00000553106.6:c.1114A>T
ENST00000307000.7:c.1099A>T
ENST00000549247.6:n.873A>T
ENST00000551114.2:n.776A>T
ENST00000553106.5:c.1114A>T
ENST00000635477.1:c.218A>T
ENST00000635528.1:n.629A>T
NM_000277.2:c.1114A>T
NM_001354304.1:c.1114A>T
NM_000277.3:c.1114A>T
NM_001354304.2:c.1114A>T

Likely Pathogenic

Met criteria codes 3

PM3_Strong PM2 PP4_Moderate

Not Met criteria codes 2

PP3 PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1114A>T (p.Thr372Ser) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 8807319, 21147011, 30050108). This variant has an extremely low frequency in gnomAD (MAF=0.00001). This variant was detected with multiple pathogenic/likely pathogenic variants: p.R408W, c.1066-11G>A (PMID: 21147011); p.A300S (PMID: 8807319); p.P281L (2 patients, LP), delF39 (PMID: 10947211). Computational evidence is conflicting. 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.

Met criteria codes

PM3_Strong	✔	Seen with 5 pathogenic variants: R408W, IVS10-11G>A (parental analysis not reported, PMID: 21147011); A300S (parental analysis not reported, PMID: 8807319); P281L (2 patients, LP), delF39 (P 5 submitters) parental analysis not reported PMID: 10947211 2.5 pts
		Seen in 1 patient, homozygous. Seen in 2nd patient with R408W (VarID577, Pathogenic). Seen in 3rd patient with IVS10-11G>A (VarID607, Pathogenic). PubMed:21147011 Proband 33: A300S (VarID92751, Pathogenic)/T372S PubMed:8807319
PM2	✔	Absent from ExAC, 1000G, ESP. Extremely low frequency in gnomAD (MAF=0.00001)
PP4_Moderate	✔	T372S was found in 1 Turkish patient with HPA (PMID: 8807319), and 3 PKU patients where BH4 deficiency had been ruled out by assessment of PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 21147011; 1 CHinese patient with MHP, dihydropteridine reductase activity, urinary biopterin and neopterin ratio were assessed PMID: 30050108 2.5 pts
		588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). T372S was found in 3 patients. PubMed:21147011 Single-strand conformational analysis was used to screen for genetic defects in all thirteen exons of the phenylalanine hydroxylase gene (PAH) in phenylketonuria and hyperphenylalaninemia patients in the Netherlands. Exons that showed a bandshift were sequenced directly. T372S was identified in 1 Turkish patient with HPA. PubMed:8807319

Not Met criteria codes

PP3	✖	Conflicting predictions of pathogenicity: deleterious in SIFT and MutationTaster, benign in Polyphen2, REVEL=0.908
PM5	✖	This variant is the only variant found in this codon in ClinVar.

Curation History

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene

No matching records found