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_001354304.2:c.1084C>T

Version: 1.0

CA6748745

1810381 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e6f92dc4-515e-4f21-a00a-a068781a7c73
Approved on: 2022/12/9
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HGVS expressions

NM_001354304.2:c.1084C>T
NC_000012.12:g.102843761G>A
CM000674.2:g.102843761G>A
NC_000012.11:g.103237539G>A
CM000674.1:g.103237539G>A
NC_000012.10:g.101761669G>A
NG_008690.1:g.78842C>T
NG_008690.2:g.119650C>T
ENST00000553106.6:c.1084C>T
ENST00000307000.7:c.1069C>T
ENST00000549247.6:n.843C>T
ENST00000551114.2:n.746C>T
ENST00000553106.5:c.1084C>T
ENST00000635477.1:c.188C>T
ENST00000635528.1:n.599C>T
NM_000277.1:c.1084C>T
NM_000277.2:c.1084C>T
NM_001354304.1:c.1084C>T
NM_000277.3:c.1084C>T

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM3 PM2

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1084C>T (p.Pro362Ser) variant in PAH was reported in a patient with classic PKU in trans with the pathogenic variant p.Arg413Pro (PMID: 28982351). This variant was present at an extremely low frequency in ExAC and absent in the gnomAD population database.

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, PM2, PP3, PP4.

Met criteria codes

PP3	✔	Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster). REVEL=0.796
PP4	✔	Variant was detected in a patient affected with cPKU. Variable sites in patient genes were aligned with the corresponding sites from the respective parents. This was seen in trans with a pathogenic variant listed in ClinVar. Those with BH4 cofactor deficiency were excluded PMID: 28982351
PM3	✔	This variant was detected in trans with the ClinVar reported pathogenic variant p.Arg413Pro in a patient with cPKU (PMID: 28982351). points=1.
PM2	✔	Present in European (non-Finnish) populations at a frequency of 0.00001 (ExAC). This variant is absent from the population database gnomAD.

Not Met criteria codes

PM5	✖	Tother variants one likely pathogenic (p.P362R) and one uncategorized (p.P362T) have been documented in ClinVar at this amino acid residue.

Curation History

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