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_000277.2(PAH):c.1172G>C (p.Ser391Thr)

Version: 1.0

CA357240

225136 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1090b77b-cd07-48e8-8b33-b7e9ceb00977
Approved on: 2020/3/7
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HGVS expressions

NM_000277.2:c.1172G>C
NM_000277.2(PAH):c.1172G>C (p.Ser391Thr)
NC_000012.12:g.102843673C>G
CM000674.2:g.102843673C>G
NC_000012.11:g.103237451C>G
CM000674.1:g.103237451C>G
NC_000012.10:g.101761581C>G
NG_008690.1:g.78930G>C
NG_008690.2:g.119738G>C
ENST00000553106.6:c.1172G>C
ENST00000307000.7:c.1157G>C
ENST00000549247.6:n.931G>C
ENST00000551114.2:n.834G>C
ENST00000553106.5:c.1172G>C
ENST00000635477.1:c.276G>C
ENST00000635528.1:n.687G>C
NM_000277.1:c.1172G>C
NM_001354304.1:c.1172G>C
NM_000277.3:c.1172G>C
NM_001354304.2:c.1172G>C

Likely Pathogenic

Met criteria codes 3
PM3 PM2 PP4_Moderate

Not Met criteria codes 2
PP3 PM5

Evidence Links 4

Expert Panel
Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1172G>C (p.Ser391Thr) variant in PAH has been reported in at least one individual with MHP (BH4 deficiency excluded, PMID: 30747360, 29499199) in trans with pathogenic variant p.Val399= (PMID: 29316886). This variant is absent in population databases. 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.

Met criteria codes

PM3	✔	Detected in trans with V399V (pathogenic 5 submitters) PMID: 29316886 Seen in trans in an individual with MHP in trans with V399V (pathogenic in database) PubMed:25894915
PM2	✔	Absent from control databases.
PP4_Moderate	✔	Seen in an individual with MHP, All patients were excluded from tetrahydrobiopterin deficiency through a BH4 loading test, a urinary pterin analysis, and a DHPR activity assay PMID: 30747360, 29499199 PubMed:29316886 PubMed:29499199 Seen in an individual with MHP, BH4 cofactor activity was not excluded. PubMed:25894915 PubMed:30747360

Not Met criteria codes

PP3	✖	Conflicting effects reported- Polyphen2: Probably Damaging. SIFT: Deleterious AND tolerated. MutationTaster: Deleterious
PM5	✖	Ser391Gly likely pathogenic

Curation History

Showing 1 to 1 of 1 rows

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