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

Version: 1.0

CA6748704

932268 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9c0b0c22-04ab-4efc-925a-41049eabfead
Approved on: 2020-05-21
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HGVS expressions

NM_001354304.2:c.1259G>T
NC_000012.12:g.102840456C>A
CM000674.2:g.102840456C>A
NC_000012.11:g.103234234C>A
CM000674.1:g.103234234C>A
NC_000012.10:g.101758364C>A
NG_008690.1:g.82147G>T
NG_008690.2:g.122955G>T
ENST00000553106.6:c.1259G>T
ENST00000307000.7:c.1244G>T
ENST00000551114.2:n.921G>T
ENST00000553106.5:c.1259G>T
ENST00000635477.1:c.363G>T
ENST00000635528.1:n.774G>T
NM_000277.1:c.1259G>T
NM_000277.2:c.1259G>T
NM_001354304.1:c.1259G>T
NM_000277.3:c.1259G>T

Likely Pathogenic

Met criteria codes 4

PM3 PM2 PP3 PP4_Moderate

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1259G>T (p.Arg420Met) variant in PAH has been reported in 1 Spanish patient with mild hyperphenylalaninemia (BH4 deficiency excluded) (PP4_Moderate; PMID: 27121329). This variant was detected with p.A403V (Pathogenic in ClinVar, VarID:92731, 18 submitters) (PM3; PMID: 27121329). This variant has a MAF of 0.00002 in population databases (PM2). This variant is predicted deleterious by SIFT, PolyPhen2, MutationTaster, and REVEL = 0.835 (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_Moderate, PP3, PM3.

Met criteria codes

PM3	✔	PMID: 27121329 - R420M detected with A403V (Pathogenic in ClinVar, VarID:92731, 18 submitters), phase known (segregation analysis performed) - 1.0 points PubMed:27121329
PM2	✔	MAF across gnomAD, ExAC, 1000 Genomes and ESP = 0.00002 in European (Non-Finnish) population; gnomAD MAF = 0.00001758 (European Non-Finnish)
PP3	✔	Predicted deleterious by SIFT, PolyPhen2, MutationTaster, and REVEL = 0.835.
PP4_Moderate	✔	PMID: 27121329 - R420M detected in Spanish patient with mild hyperphenylalaninemia (Phe > 120 umol/L), BH4 deficiency ruled out via urinary pterin analysis PubMed:23500595

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View		Likely Pathogenic	Phenylketonuria	2020-05-21	1.0	-	PAH

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