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.1246C>A

Version: 2.0

CA16020980

987913 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 04c30910-babe-4e4b-a469-d820d4147268
Approved on: 2024/11/17
Published on: 2024/11/18

HGVS expressions

NM_001354304.2:c.1246C>A
NC_000012.12:g.102840469G>T
CM000674.2:g.102840469G>T
NC_000012.11:g.103234247G>T
CM000674.1:g.103234247G>T
NC_000012.10:g.101758377G>T
NG_008690.1:g.82134C>A
NG_008690.2:g.122942C>A
ENST00000553106.6:c.1246C>A
ENST00000307000.7:c.1231C>A
ENST00000551114.2:n.908C>A
ENST00000553106.5:c.1246C>A
ENST00000635477.1:c.350C>A
ENST00000635528.1:n.761C>A
NM_000277.1:c.1246C>A
NM_000277.2:c.1246C>A
NM_001354304.1:c.1246C>A
NM_000277.3:c.1246C>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PM2_Supporting | PP3_Strong | PM5_Supporting | PP4

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1246C>A (p.Pro416Thr) variant in PAH has been reported in 1 patient with mild non-PKU HPA with Phe = 246-420umol/L (BH4 deficiency not excluded) (PP4; PMID: 9380432). It has been reported in unknown phase with the pathogenic p.R408Q variant (ClinVar ID: 577) (PM3_Supporting). This variant is absent from the population database gnomAD v2.1.1. (PM2_Supporting). This variant is predicted to be deleterious by REVEL (score 0.965) (PP3_Strong). A different missense variant at the same site, p.Pro416Gln, has been classified as likely pathogenic in ClinVar by the PAH VCEP (ID: 558091, PM5_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: PM2_Supporting, PM3_Supporting, PP3_Strong, PP4, PM5_supporting.

Met criteria codes

PM3_Supporting	✔	PMID: 32668217: 1 case with PAH deficiency (no further specification), in unknown phase with path variant p.R408Q (ClinVar ID: 577) (0.5pts)
PM2_Supporting	✔	Variant absent from population database gnomAD v4.1.0
PP3_Strong	✔	Predicted deleterious by SIFT, PolyPhen2, MutationTaster, and REVEL = 0.965.
PM5_Supporting	✔	c.1246A>T (p.Pro416Gln) is likely path by PAH VCEP in ClinVar (ID: 558091)
PP4	✔	PMID: 9380432 - P416T detected with mild non-PKU HPA, plasma Phe = 246-420umol/L on unrestricted diet, BH4 deficiency not excluded (number of patients/alleles not specified) - see Figure 1

Curation History

Showing 1 to 2 of 2 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.