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.922C>G (p.Leu308Val)

Version: 1.0

CA229849

102895 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 220a2761-ff28-4e58-a382-7a56bab8d9dd
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000277.1(PAH):c.922C>G (p.Leu308Val)
NM_000277.1:c.922C>G
NC_000012.12:g.102846942G>C
CM000674.2:g.102846942G>C
NC_000012.11:g.103240720G>C
CM000674.1:g.103240720G>C
NC_000012.10:g.101764850G>C
NG_008690.1:g.75661C>G
NG_008690.2:g.116469C>G
ENST00000553106.6:c.922C>G
ENST00000307000.7:c.907C>G
ENST00000549247.6:n.681C>G
ENST00000551114.2:n.584C>G
ENST00000553106.5:c.922C>G
ENST00000635477.1:c.74-2511C>G
ENST00000635528.1:n.437C>G
NM_000277.2:c.922C>G
NM_001354304.1:c.922C>G
NM_000277.3:c.922C>G
NM_001354304.2:c.922C>G

Likely Pathogenic

Met criteria codes 5

PM3 PP3_Moderate PP4 PM2_Supporting PS3_Supporting

Evidence Links 2

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 NM_000277.1(PAH):c.922C>G (p.Leu308Val) variant is a missense variant in exon 9/13 of PAH. The variant has been found to reduce PAH enzymatic activity to 15-19% versus wild type PAH enzyme in transfected COS cells (PMID: 18590700). The variant has been previously reported in confirmed trans with the c.1315+1G>A variant (Pathogenic per ClinGen PAH VCEP) in a patient with mild PKU (plasma Phe 600-900 umol/L); BH4 deficiency does not appear to have been excluded (PMID: 26542770). The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP. The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.892). Classification: Likely Pathogenic Supporting Criteria: PS3_supporting; PM2_supporting; PM3; PP4; PP3_moderate

---

Met criteria codes

PM3	✔	Single patient c.1315+1G>A (pathogenic in ClinVar) / c.922C>G with mild PKU 376 patients in Denmark, represents all patients diagnosed with PKU between 1967-2014. PubMed:26542770
PP3_Moderate	✔	All databases agree on damaging effect. REVEL = 0.892
PP4	✔	Single patient with mild PKU (values 600-900). No specific level provided.
PM2_Supporting	✔	not found in gnomAD v2.1.1
PS3_Supporting	✔	Enzyme activity = 19% (PMID: 18590700) PAH activity analysis. Site directed mutagenesis, transfected COS-1 cells. Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. Use both standard cDNA expression system and a new Intinic plasmid system which incorporates intronic sequences. Standard cDNA method demonstrates 15% and intinic system demonstrates 19% residual enzyme activity. PubMed:18590700

Curation History

Showing 1 to 1 of 1 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.