

Variant: NM_000277.1(PAH):c.508C>G (p.His170Asp)

CA273111 [↗](#)

92744 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 8845817f-fc6b-4d7f-93b6-a072ae8c8c8a

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HGVS expressions

NM_000277.1(PAH):c.508C>G (p.His170Asp)

NM_000277.1:c.508C>G

NC_000012.12:g.102866597G>C

CM000674.2:g.102866597G>C

NC_000012.11:g.103260375G>C

CM000674.1:g.103260375G>C

NC_000012.10:g.101784505G>C

NG_008690.1:g.56006C>G

NG_008690.2:g.96814C>G

NM_000277.2:c.508C>G

NM_001354304.1:c.508C>G

NM_000277.3:c.508C>G

ENST00000307000.7:c.493C>G

ENST00000549111.5:n.604C>G

ENST00000551988.5:n.530+10865C>G

ENST00000553106.5:c.508C>G

Pathogenic

Met criteria codes **5**

PM3_Strong

PP3

PP4

PM2

PS3

Evidence Links **3**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.508C>G (p.His170Asp) variant in PAH has been reported in 1 patient with hyperphenylalaninemia, and 1 patient with benign persistent hyperphenylalaninemia. (PP4; PMID: 11385716). This variant has an extremely low allele frequency (0.00018) in gnomAD (PM2; <http://gnomad.broadinstitute.org>). This variant has 43% enzyme activity (PS3; PMID: 17935162). This variant was detected in trans with R261X, c.60+5G>T, c.1315+1G>A (Pathogenic in ClinVar) (PM3_Strong; PMID: 11385716; PMID: 24941924). Computational prediction tools and conservation analysis suggest that the c.829T>G variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3, PM3_Strong

Met criteria codes

PM3_Strong			Detected in trans with R261X, c.60+5G>T, c.1315+1G>A (known pathogenic variants) PMID: 11385716; PMID: 24941924
H170D was present in 2 Hispanics whose genotypes were H170D/H170D and H170D/R261X. PubMed:11385716  c.508C>G/c.60+5G>T (VarID:102751, Pathogenic); c.508C>G/c.1315+1G>A (VarID:576, Pathogenic); c.508C>G/c.842+1G>A (VarID599, P/LP) PubMed:24941924 			
PP3			Predicted deleterious in SIFT, Polyphen2, MutationsTaster. REVEL=0.938
PP4			H170D present in 1 patient with HPA, and 1 patient with benign persistent HPA. PMID: 11385716
H170D was present in 2 Hispanics with PKU. one with hyperphenylalaninemia (R261X/H170D genotype), the other with benign persistent hyperphenylalaninemia (homozygous H170D). PubMed:11385716 			
PM2			Absent in ExAC, 1000G, ESP. Extremely low frequency in gnomAD (0.00018)
PS3			43% residual enzyme activity PMID: 17935162
43% residual enzyme activity PubMed:17935162 			

Curation History

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