

Variant: *NM_000277.2(PAH):c.1163T>C (p.Val388Ala)*

Version: 1.0

CA267628 [↗](#)

120260 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 4a58fdc9-98c8-41a1-90fc-e0e94d381492

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HGVS expressions

NM_000277.2:c.1163T>C

NM_000277.2(PAH):c.1163T>C (p.Val388Ala)

NC_000012.12:g.102843682A>G

CM000674.2:g.102843682A>G

NC_000012.11:g.103237460A>G

CM000674.1:g.103237460A>G

NC_000012.10:g.101761590A>G

NG_008690.1:g.78921T>C

NG_008690.2:g.119729T>C

ENST00000553106.6:c.1163T>C

ENST00000307000.7:c.1148T>C

ENST00000549247.6:n.922T>C

ENST00000551114.2:n.825T>C

ENST00000553106.5:c.1163T>C

ENST00000635477.1:c.267T>C

ENST00000635528.1:n.678T>C

NM_000277.1:c.1163T>C

NM_001354304.1:c.1163T>C

NM_000277.3:c.1163T>C

NM_001354304.2:c.1163T>C

Likely Pathogenic

Met criteria codes **4**

PP3

PP4

PM2

PM5

Not Met criteria codes **1**

PM3

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1163T>C (p.Val388Ala) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120260); the collection method is stated as “literature only” and no further information is provided. With respect to the published literature, it has been previously reported in a French proband classified as having mild PKU (defined by the authors as plasma phenylalanine levels between 600-1200uL/L) (PMID: 26666653); formal testing to exclude BH4 deficiency was not noted (PP4). The proband was said to be heterozygous for the variant and also harbor the known pathogenic (per ClinGen PAH working group classification, see ClinVar ID 92731) c.1208C>T (Ala403Val); however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. Thus, at this point, PM3 cannot be applied with full confidence. The variant results in the substitution of a moderately conserved Valine residue with Alanine, a physiochemically similar amino acid. However, the amino acid substitution is predicted damaging by multiple lines of computational evidence e.g., Predicted deleterious in SIFT, Polyphen2, Mutation Taster. REVEL= 0.919) (PP3). It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). Other missense changes at this Valine residue (Val388) have been previously reported Pathogenic or Likely Pathogenic in ClinVar, e.g., p.Val388Met (Pathogenic per internal PAH ClinGen Working Group classification, ClinVar ID 619), as well as p.Val388Leu (PM5). The c.181A>G (p.Asn61Asp) variant in PAH has been reported in 1 individual with mild PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 12501224). This variant is absent in population databases (PM2). This variant was detected with p.R261Q (Pathogenic/likely pathogenic in ClinVar) (PM3; PMID: 12501224). 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, PM2, PM5, PP3.

Met criteria codes

PP3	 	The variant results in the substitution of a moderately conserved Valine residue with Alanine, a physiochemically similar amino acid. However, the amino acid substitution is predicted damaging by multiple lines of computational evidence e.g., Predicted deleterious in SIFT, Polyphen2, Mutation Taster. REVEL= 0.919) (PP3).
PP4	 	The c.1163T>C (p.Val388Ala) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120260); the collection method is stated as “literature only” and no further information is provided. With respect to the published literature, it has been previously reported in a French proband classified as having mild PKU (defined by the authors as plasma phenylalanine levels between 600-1200uL/L) (PMID: 26666653); formal testing to exclude BH4 deficiency was not noted (PP4). The proband was said to be heterozygous for the variant and also harbor the known pathogenic (per ClinGen PAH working group classification, see ClinVar ID 92731) c.1208C>T (Ala403Val); however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. Thus, at this point, PM3 cannot be applied with full confidence. The c.1163T>C (p.Val388Ala) variant in PAH has been previously reported Likely Pathogenic by one clinical laboratory in ClinVar (see variant ID 120260); the collection method is stated as “literature only” and no further information is provided. With respect to the published literature, it has been previously reported in a French proband classified as having mild PKU (defined by the authors as plasma phenylalanine levels between 600-1200uL/L) (PMID: 26666653); formal testing to exclude BH4 deficiency was not noted (PP4). The proband was said to be heterozygous for the variant and also harbor the known pathogenic (per ClinGen PAH working group classification, see ClinVar ID 92731) c.1208C>T (Ala403Val); however, the manuscript did not specify whether the phase of the variants was confirmed via parental testing. Thus, at this point, PM3 cannot be applied with full confidence. PubMed:26666653 
PM2		It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).
PM5	 	Other missense changes at this Valine residue (Val388) have been previously reported Pathogenic or Likely Pathogenic in ClinVar, e.g., p.Val388Met (Pathogenic per internal PAH ClinGen Working Group classification, ClinVar ID 619), as well as p.Val388Leu (PM5).

Not Met criteria codes

PM3



No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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