

Variant: NM_000277.2(PAH):c.434A>T (p.Asp145Val)

CA229539 [↗](#)

102667 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6ebfc9b5-513f-4058-98a8-49294b98dd36

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HGVS expressions

NM_000277.2(PAH):c.434A>T (p.Asp145Val)

NM_000277.2:c.434A>T

NC_000012.12:g.102877469T>A

CM000674.2:g.102877469T>A

NC_000012.11:g.103271247T>A

CM000674.1:g.103271247T>A

NC_000012.10:g.101795377T>A

NG_008690.1:g.45134A>T

NG_008690.2:g.85942A>T

NM_000277.1:c.434A>T

NM_001354304.1:c.434A>T

NM_000277.3:c.434A>T

ENST00000307000.7:c.419A>T

ENST00000549111.5:n.530A>T

ENST00000550978.6:n.418A>T

ENST00000551988.5:n.523A>T

ENST00000553106.5:c.434A>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM2

PM3_Strong

Not Met criteria codes **1**

PM5

Evidence Links **7**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.434A>T (p.Asp145Val) PAH variant has been identified in patients with PAH deficiency from the US, Germany, Italy and Spain. BH4 deficiency was excluded. (PMID: 8659548; 11385716; 12655553; 17096675; 23514811) It was detected with known pathogenic variants: V388M (PMID: 8659548), I65T (PMID: 24368688), and R408W (PMID: 26666653). It is found at extremely low frequency (MAF 0.00012 in

gnomAD). A deleterious effect is predicted in SIFT, Polyphen2, MutationTaster, and REVEL=0.987. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PP4_Moderate, PP3

Met criteria codes

PP4_Moderate			<p>D145V has been identified patients with PAH deficiency from the US, Germany, Italy and Spain. BH4 deficiency excluded. PMID: 8659548; 11385716; 12655553; 17096675; 23514811.</p> <p>Forty newborns ascertained by the Texas Newborn Screening Program due to phenylalanine (PHE) levels in serum above 4 mg/dl were blinded and studied. The diagnosis of classic PKU was done in cases with the untreated level of PHE > 20 mg/dl (1200 µM), normal level of Biopterin and the tyrosine level < 3 mg/dl. D145V identified on 1 chromosome. PubMed:11385716</p> <p>126 HPA patients from Southern Italy who were identified in a neonatal screening program. D145V identified in a mild HPA patient. PubMed:17096675</p> <p>226 German families with PAH deficiency, most of them from Southern Germany. D145V seen on 2 alleles. PubMed:12655553</p> <p>149 hyperphenylalaninemic females were diagnosed by blood Phe, blood tyrosine, and metabolites in urine. D145V identified in 1 patient with MHP (380 umol/l). PubMed:8659548</p> <p>We detected in this period 179 patients (78 male and 91 female) of the Andalusian community whose cut-off value for phenylalanine is 180 mM. Patients with transient HPA (two patients) or with HPA due to a defect in the synthesis or recycling of the cofactor BH4 (two patients) were excluded. D145V seen on 1 allele. PubMed:23514811</p>
PP3			<p>Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.987</p>
PM2			<p>Extremely low frequency: MAF 0.00012 in gnomAD.</p>
PM3_Strong			<p>Detected with known pathogenic variants: V388M (PMID: 8659548), I65T (PMID: 24368688), and R408W (PMID: 26666653).</p> <p>Patient 8 genotype: p.I65T/p.D145V PubMed:24368688</p> <p>Patient I/1140/LMA-10: Allele1: D145V, Allele 2: V388M (Pathogenic in ClinVar). PubMed:8659548</p> <p>Genotype: c. [434A>T]; [1222C>T]/p. [Asp145Val];[Arg408Trp] PubMed:26666653</p>

Not Met criteria codes

PM5			<p>only variant found in this codon in ClinVar</p>
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Curation History [↗](#)

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