

Variant: NM_000277.2(PAH):c.856G>A (p.Glu286Lys)

CA229826 [↗](#)

102880 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 4dc6bb14-c14b-4cd7-854f-bb6dab99dc54

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HGVS expressions

NM_000277.2(PAH):c.856G>A (p.Glu286Lys)

NM_000277.2:c.856G>A

NC_000012.12:g.102851743C>T

CM000674.2:g.102851743C>T

NC_000012.11:g.103245521C>T

CM000674.1:g.103245521C>T

NC_000012.10:g.101769651C>T

NG_008690.1:g.70860G>A

NG_008690.2:g.111668G>A

NM_000277.1:c.856G>A

NM_001354304.1:c.856G>A

NM_000277.3:c.856G>A

ENST00000307000.7:c.841G>A

ENST00000549247.6:n.615G>A

ENST00000551114.2:n.518G>A

ENST00000553106.5:c.856G>A

ENST00000635477.1:n.17G>A

Pathogenic

Met criteria codes **5**

PS3

PP3

PM3

PM2

PP4_Moderate

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.856G>A (p.Glu286Lys) variant in PAH is present with low frequency in population databases (1.2e-4), and is predicted to be deleterious using in silico algorithms. It has been identified in trans with pathogenic variants in two independent patients (R243Q, R241C), and has been identified in a patients with Phenylketonuria in which a defect in BH4 metabolism has been excluded (PMID: 14722928, 24401910). Enzyme activity has been measured as 1% of wild type controls (BioPKU). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PP4_Moderate, PS3, PP3.

Met criteria codes

PS3		✓	Enzyme activity 1% per BioPKU
PP3		✓	in silico agree on damaging effect REVEL=0.971
PM3		✓	Two independent patients reported, one in trans with R243Q and classic PKU, and one in trans with R241C and mild PKU
			Two independent patients reported, one in trans with R243Q and classic PKU, and one in trans with R241C and mild PKU PubMed:14722928 
PM2		✓	Allele Frequency: 0.00012
PP4_Moderate		✓	BH4 defect excluded in all patients. One patient with classic PKU (Phe=1665umol/L) and one with mild PKU (Phe=610umol/L) (PMID: 14722928). An additional patient with this variant reported with classic PKU (PMID: 24401910)
			BH4 defect excluded in all patients. One patient with classic PKU (Phe=1665umol/L) and one with mild PKU (Phe=610umol/L) PubMed:14722928  Single patient with classic PKU PubMed:24401910 

Curation History

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