

Variant: *NM_000277.2(PAH):c.250G>T (p.Asp84Tyr)*

Version: 1.0

CA229500 [↗](#)

102639 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: fc7cd29b-7604-4db2-9477-5b5ad6389513

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HGVS expressions

NM_000277.2:c.250G>T

NM_000277.2(PAH):c.250G>T (p.Asp84Tyr)

NC_000012.12:g.102894837C>A

CM000674.2:g.102894837C>A

NC_000012.11:g.103288615C>A

CM000674.1:g.103288615C>A

NC_000012.10:g.101812745C>A

NG_008690.1:g.27766G>T

NG_008690.2:g.68574G>T

ENST00000553106.6:c.250G>T

ENST00000307000.7:c.235G>T

ENST00000546844.1:c.250G>T

ENST00000548677.2:n.337G>T

ENST00000548928.1:n.172G>T

ENST00000549111.5:n.346G>T

ENST00000550978.6:c.234G>T

ENST00000551337.5:c.250G>T

ENST00000551988.5:n.339G>T

ENST00000553106.5:c.250G>T

NM_000277.1:c.250G>T

NM_001354304.1:c.250G>T

NM_000277.3:c.250G>T

NM_001354304.2:c.250G>T

Pathogenic

Met criteria codes **4**

PM2_Supporting

PM3_Very Strong

PP4_Moderate

PP3

Evidence Links **6**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.250G>T (p.Asp84Tyr) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 9634518). This variant has an extremely low allele frequency (MAF=0.00002) in gnomAD. This variant was detected with multiple pathogenic variants: F39L (PMID:11328945), Y356X (PMID: 15503242), P281L (PMID: 23430918), R158Q (PMID: 19609714) (PM3_VS). Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster, REVEL=0.819) (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_VS, PM2_supporting, PP4_Moderate, PP3.

Met criteria codes

PM2_Supporting			Extremely low frequency in gnomAD (MAF=0.00002)
PM3_Very Strong			Detected with F39L (P) PMID:11328945, Y356X (P/LP) PMID: 15503242, P281L (P) PMID: 23430918, R158Q (P) PMID: 19609714 Maternal PAH genotype: F39L/D84Y (VarID605, pathogenic) PubMed:11328945 Patient genotype: [D84Y] + [R158Q] (VarID 587, pathogenic) PubMed:19609714 mutant PAH Genotype p.D84Y: p.P281L (VarID589, pathogenic) PubMed:23430918 When available, parental DNA samples were sequenced to confirm trans configurations in compound heterozygotes and to distinguish homozygosity from hemizygosity. Patient 38: PAH allele 1 D84Y; PAH allele 2 Y356X (VarID 595, P/LP) PubMed:15503242
PP4_Moderate			D84Y was detected in 1 patient with classic PKU. Exclusion of a defect in tetrahydrobiopterin metabolism. PMID: 9634518 Seven centers in France, Italy, Belgium, Germany, and Denmark participated in this collaborative study. In all patients, hyperphenylalaninemia had been detected by national mass screening programs, and PAH deficiency had been assessed after exclusion of a defect in tetrahydrobiopterin metabolism. D84Y was detected in 1 patient with classic PKU. PubMed:9634518 One hundred forty-nine patients enrolled in the Maternal PKU Collaborative Study were subjects. They all had normal blood tyrosine concentrations. D84Y was detected on 1 chromosome. PubMed:8659548
PP3			Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster, REVEL=0.819)

Curation History 

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