

Variant: NM_000277.2(PAH):c.818C>T (p.Ser273Phe)

CA229785 [↗](#)

598 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 75b9eddc-e554-4f4c-91a7-976ac6c27ba2

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HGVS expressions

NM_000277.2(PAH):c.818C>T (p.Ser273Phe)

NM_000277.2:c.818C>T

NC_000012.12:g.102852839G>A

CM000674.2:g.102852839G>A

NC_000012.11:g.103246617G>A

CM000674.1:g.103246617G>A

NC_000012.10:g.101770747G>A

NG_008690.1:g.69764C>T

NG_008690.2:g.110572C>T

NM_000277.1:c.818C>T

NM_001354304.1:c.818C>T

NM_000277.3:c.818C>T

ENST00000307000.7:c.803C>T

ENST00000549247.6:n.577C>T

ENST00000553106.5:c.818C>T

Likely Pathogenic

Met criteria codes **4**

PM3_Strong

PP3

PM2

PP4_Moderate

Not Met criteria codes **1**

PM5

Evidence Links **4**

Expert Panel

[Phenylketonuria VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM2: Extremely low frequency in ExAC and gnomAD (1 allele); PP3: Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.978; PP4_Moderate: S273F was detected in in Northern Ireland, Belgium/French, Western Scotland, and New South Wales PKU patients. BH4 deficiency was assessed in 1 study. Upgraded per ClinGen Metabolic workgroup. (PMID:1671881; PMID:8533759; PMID:9012412; PMID:24368688); PM3_Strong: Seen with 2 known pathogenic mutations: I65T, R408W. Upgraded based on SVI workgroup recommendations and approved PAH guidelines (PMID:24368688). In summary this variant meets criteria

to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM2, PP3, PP4_Moderate, PM3_Strong).

Met criteria codes

PM3_Strong			Seen with 2 known pathogenic mutations: I65T, R408W. Upgraded based on SVI worgroup recommendations and approved PAH guidelines
Patient 32 genotype: I65T/ S273F. Patient 111 genotype: S273F/ R408W. PubMed:24368688 			
PP3			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.978
PM2			Extremely low frequency in ExAC and gnomAD (1 allele)
PP4_Moderate			S273F was detected in in Northern Ireland, Belgium/French, Western Scotland, and New South Wales PKU patients. BH4 deficiency was assessed in 1 study. Upgraded per ClinGen Metabolic workgroup. The five patients reported here were born either in Belgium (four patients) or in north eastern France (one patient). All five children were diagnosed through systematic newborn screening programmes and met the criteria for typical PKU (low tolerance for dietary phenylalanine, averaging 250 mg/day). The abolition of an invariant BamHI site located in the coding sequence of the PAH gene (exon 7) led to the recognition of two new point mutations at codon 272 and 273 (272gly----stop and 273ser----phe, respectively). PubMed:1671881  One hundred and eleven patients, including seven families with two or more affected individuals, were recruited from the records of the NSW Newborn Screening Programme or from the PKU Clinic at the Children’s Hospital at Westmead, Sydney Australia. p.S273F was detected in 2 patients. PubMed:24368688  PKU patients from four centers in three countries of Great Britain were studied. S273F was detected on 2 Western Scotland alleles. PubMed:9012412  A total of 121 Northern Irish families with HPA (111 with PKU and 10 with MHP) were investigated, including virtually all patients born after 1972. dihydrobiopterin reductase deficiency was excluded. S273F was seen on 3 alleles. PubMed:8533759 

Not Met criteria codes

PM5			S273F is the only variant in this codon in ClinVar
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Curation History 

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