

Variant: *NM_000277.1:c.875C>T*

Version: 1.0

CA16020882 [↗](#)

626282 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 3f9695f4-a4fc-4c00-af32-1cac6e4e001f

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HGVS expressions

NM_000277.1:c.875C>T

NC_000012.12:g.102851724G>A

CM000674.2:g.102851724G>A

NC_000012.11:g.103245502G>A

CM000674.1:g.103245502G>A

NC_000012.10:g.101769632G>A

NG_008690.1:g.70879C>T

NG_008690.2:g.111687C>T

ENST00000553106.6:c.875C>T

ENST00000307000.7:c.860C>T

ENST00000549247.6:n.634C>T

ENST00000551114.2:n.537C>T

ENST00000553106.5:c.875C>T

ENST00000635477.1:c.36C>T

NM_000277.2:c.875C>T

NM_001354304.1:c.875C>T

NM_000277.3:c.875C>T

NM_001354304.2:c.875C>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM3_Strong

PM2

Evidence Links **5**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.875C>T (p.Pro292Leu) variant in PAH has been reported in multiple individuals with mild PKU (BH4 deficiency excluded). (PMID: 26503515, 24705691, 29413232). This variant has extremely low frequency in gnomAD (MAF=0.00006). This variant was detected in trans with pathogenic variants c.913-7A>G (PMID: 26322415) and p.Arg243Gln (PMID: 31178897). Computational evidence support a deleterious

effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PP3.

Met criteria codes

PP4_Moderate			Seen in multiple patients with PKU in 3 studies. One study mentioned BH4 deficiency excluded. PMID: 26503515, PMID: 24705691, PMID: 29413232 Seen in an individual with PAH-defecient PKU, Methods state serum Phe concentrations ofthese patients fell in a range from 360 mmol/L to 1800 mmol/L. PubMed:29413232  Seen in a individual with diagnosed PKU, no other information provided. From a 'core' family meaning a completed pedigree. No consanguineous families were included in this study PubMed:24705691  Seen in an individual with PKU. A total of 796 unrelated patients from 29 separate newborn screening centres of China were enrolled. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515 
PP3			Multiple lines predict deleterious effect. Predicted deleterious by SIFT, probably damaging by Polyphen and Disease causing by MutationTaster.
PM3_Strong			Detected in trans with c.913-7A>G (LP) confirmed by analyzing parental DNA PMID: 26322415 and p.Arg243Gln detected with Trio-WES (P 10 submitters) PMID: 31178897 PubMed:26322415  PubMed:31178897 
PM2			Absent from 1000G and Exac. Low freq in gnomAD (MAF=0.00006)

Curation History

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