

Variant: NM_001354304.2:c.684A>C

Version: 2.0

CA386296575 [↗](#)

1065380 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 33ecfb68-253a-4ef9-a345-1da8c398b15d

Approved on: 2024/9/6

Published on: 2024/9/6

HGVS expressions

NM_001354304.2:c.684A>C

NC_000012.12:g.102855158T>G

CM000674.2:g.102855158T>G

NC_000012.11:g.103248936T>G

CM000674.1:g.103248936T>G

NC_000012.10:g.101773066T>G

NG_008690.1:g.67445A>C

NG_008690.2:g.108253A>C

ENST00000553106.6:c.684A>C

ENST00000307000.7:c.669A>C

ENST00000549111.5:n.780A>C

ENST00000553106.5:c.684A>C

NM_000277.1:c.684A>C

NM_000277.2:c.684A>C

NM_001354304.1:c.684A>C

NM_000277.3:c.684A>C

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM3

PM2_Supporting

Not Met criteria codes **1**

PM5

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.684A>C (p.Glu228Asp) variant in PAH is a missense variant in exon 6/13 that is predicted damaging by REVEL (REVEL score 0.688) (PP3_Supporting). It has been previously reported in one individual with PAH deficiency (960μmol/L Phe) with BH4 cofactor deficiency

excluded (PMID: 28982351) (PP4_Moderate), who harbored it in trans with the known pathogenic/likely pathogenic variant p.Arg243Gln (ClinVar ID 591) (1pt; PM3_Moderate). A different missense variant at the same site, p.Glu228Lys, is classified as a VUS in ClinVar by the PAH VCEP (ID 120284); thus PM5 is not met. This variant is absent from gnomAD v2.1.1 (PM2_Supporting). In summary, this variant meets criteria to be classified as Likely Pathogenic based on the ACMG/AMP criteria applied, as specified by the ClinGen Phenylketonuria Variant Curation Expert Panel (Specifications Version 2.0): PM2_Supporting, PM3_Moderate, PP4_Moderate, PP3_Supporting.

Met criteria codes

PP4_Moderate			This variant was documented 1 time in a patient with PAH deficiency (960μmol/L Phe) in the Han Chinese population (PMID: 28982351), Patients with BH4 cofactor deficiency were excluded
PP3			REVEL=0.688
PM3			This variant was detected in trans with the pathogenic PAH variant p.Arg243Gln (path/likely path per multiple submitters, ClinVar ID 591) (1.0pt) PMID: 28982351
PM2_Supporting			This variant is absent from population databases gnomAD, 1000 Genomes, and ESP.

Not Met criteria codes

PM5			p.Glu228Lys is classified as VUS by PAH VCEP in ClinVar (id 120284)
-----	--	---	---

Curation History

▼

▼

Showing 1 to 5 of 5 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.