The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.2(PAH):c.794G>A (p.Cys265Tyr)

Version: 1.0

CA229763

102836 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: cd09d332-2e68-426f-a5a2-6f716599b375
Approved on: 2022/2/25
Published on: 2022/4/16

HGVS expressions

NM_000277.2:c.794G>A
NM_000277.2(PAH):c.794G>A (p.Cys265Tyr)
NC_000012.12:g.102852863C>T
CM000674.2:g.102852863C>T
NC_000012.11:g.103246641C>T
CM000674.1:g.103246641C>T
NC_000012.10:g.101770771C>T
NG_008690.1:g.69740G>A
NG_008690.2:g.110548G>A
ENST00000553106.6:c.794G>A
ENST00000307000.7:c.779G>A
ENST00000549247.6:n.553G>A
ENST00000553106.5:c.794G>A
NM_000277.1:c.794G>A
NM_001354304.1:c.794G>A
NM_000277.3:c.794G>A
NM_001354304.2:c.794G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PP3 PM2 PS3_Supporting

Not Met criteria codes 2

PM3 PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.794G>A (p.Cys265Tyr) variant in PAH is reported in a Japanese patient with phenylketonuria (BH4 deficiency excluded, PMID: 9860305). This variant is absent from population databases. Multiple lines of computational evidence support a deleterious effect. PAH activity in COS cell expression system was 0% (PMID: 9860305). In summary, this variant meets the criteria to be classified as Likely

pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH VCEP: PP4_moderate, PM2, PS3_supporting, PP3.

Met criteria codes

PP4_Moderate	✔	Detected in a Japanese patient with PKU. Patients with BH4 deficiency were excluded based on the absence of neurologic deterioration on a low phenylalanine diet, analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test, and/or pteridine analysis of urine. PMID: 9860305
PP3	✔	computational evidence supports deleterious effect: Damaging in SIFT, MutationTaster; Probably damaging in PP2; REVEL=0.913.
PM2	✔	Not found in ExAC/gnomAD or 1000 genomes.
PS3_Supporting	✔	PAH activity in COS cell expression system, C265Y 0% activity PMID: 9860305. This PMID approved for PS3_Supp on PAH VCEP call 2/25/22.

Not Met criteria codes

PM3	✖	2nd allele/genotype not reported
PM5	✖	C265G has no interpretation in ClinVar

Curation History

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