

Variant: *NM_000277.3:c.494C>A*

Version: 1.0

CA16020800 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0e6abec4-a4c1-4633-9b93-f5e4f44c8890

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HGVS expressions

NM_000277.3:c.494C>A

NC_000012.12:g.102866611G>T

CM000674.2:g.102866611G>T

NC_000012.11:g.103260389G>T

CM000674.1:g.103260389G>T

NC_000012.10:g.101784519G>T

NG_008690.1:g.55992C>A

NG_008690.2:g.96800C>A

NM_000277.1:c.494C>A

NM_000277.2:c.494C>A

NM_001354304.1:c.494C>A

ENST00000307000.7:c.479C>A

ENST00000549111.5:n.590C>A

ENST00000551988.5:n.530+10851C>A

ENST00000553106.5:c.494C>A

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM3

PM2

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.494C>A (p.Ala165Asp) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 26503515). This variant is absent in population databases (PM2). This variant was detected with pathogenic variants p.R111X and p.R176X (PM3; PMID: 23225039). Computational evidence support a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP4_Moderate	 	<p>p.A165D detected in PKU patient(s). BH4 deficiency assessed. PMID: 26503515</p> <hr/> <p>p.A165D detected on 2 alleles. 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 </p>
PP3	 	<p>Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.985</p>
PM3	 	<p>Detected with R111X (P, 7 submitters) and R176X (P, 11 submitters) PMID: 23225039</p> <hr/> <p>Individuals with R111X/A165D and R176X/A165D genotypes, on the other hand, respectively presented moderate and classic PKU phenotypes. PubMed:23225039 </p>
PM2		<p>Absent from ExAC/gnomAD, 1000 Genomes, ESP</p>

Curation History 		
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