

Variant: *NM_000277.1(PAH):c.466G>C (p.Ala156Pro)*

Version: 1.0

CA229562 [↗](#)

102688 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 1d56d7cf-cc3f-4605-a126-3d23c461b8c7

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HGVS expressions

NM_000277.1(PAH):c.466G>C (p.Ala156Pro)

NM_000277.1:c.466G>C

NC_000012.12:g.102866639C>G

CM000674.2:g.102866639C>G

NC_000012.11:g.103260417C>G

CM000674.1:g.103260417C>G

NC_000012.10:g.101784547C>G

NG_008690.1:g.55964G>C

NG_008690.2:g.96772G>C

ENST00000553106.6:c.466G>C

ENST00000307000.7:c.451G>C

ENST00000549111.5:n.562G>C

ENST00000551988.5:n.530+10823G>C

ENST00000553106.5:c.466G>C

NM_000277.2:c.466G>C

NM_001354304.1:c.466G>C

NM_000277.3:c.466G>C

NM_001354304.2:c.466G>C

Pathogenic

Met criteria codes **4**

PP4_Moderate

PM2_Supporting

PM3_Very Strong

PS3_Supporting

Evidence Links **3**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen PAH Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines Version 1

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

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.466G>C (p.Ala156Pro) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). (PMID: 26322415). This variant is absent in population databases. This variant was detected in trans with multiple pathogenic variants: p.H220P (PMID 26322415); c.611A>G (aka EX6-96A>G, PMID: 26600521); p.V5Sfs*33, p.R158W, p.R241C (2 patients), p.R261Q, p.R400T, p.T418P (PMID: 30050108). Functional studies show the PAH A156P mutant produces reduced protein (8.7% of wild type), with a residual enzyme activity of 10.4% (PMID 24327145). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2_supporting, PP4_Moderate, PS3_supporting.

Met criteria codes

PP4_Moderate			p.[A156P] reported in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PMID: 26322415 PMID 26322415: listed p.[A156P];[H220P] in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded byanalysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415  PMID 19915519: phenotypes were classified based on the pretreatment plasma phenylalanine (phe) levels or the phe level at diagnosis. Accordingly, 113 patients were classic PKU (phe >1200 uM/L) (113/212); 66, mild PKU (phe 600-1200 uM/L) (66/212); 15, MHP (phe 120-600 uM/L) (15/212); 18 cases were unclassified, with their phe level unavailable. Listed in Table 2, no specific phe level specified for this patient. No comment on exclusion of BH4 deficiency. PubMed:19915519 
PM2_Supporting			Absent from controls in ExAC, 1000 Genomes, and ESP
PM3_Very Strong			PMID 26322415: detected with p.[H220P] (not in ClinVar, LP by PAH VCEP) All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing. Detected with c.611A>G (EX6-96A>G, P-6 submitters), parental analysis performed. PMID: 26600521 p.A156P/p.V5Sfs*33 (P-1), p.R158W (P-4)/p.A156P, p.R241C (P-8)/p.A156P (2 patients), p.R261Q (P-9)/p.A156P, p.A156P/p.R400T (P-1), p.A156P/p.T418P (P-1) The validation tests on parents were performed using Sanger sequencing. PMID: 30050108 Detected with p.R408Q parental analysis not reported PMID: 25894915 PMID 26322415: listed p.[A156P];[H220P] in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded byanalysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415 
PS3_Supporting			PMID 24327145: Relative quantity of PAH proteins for A156P 8.7%, the residual enzyme activity 10.4% PMID 24327145: Relative quantity of PAH proteins for A156P 8.7%, the residual enzyme activity 10.4% PubMed:24327145 

Curation History 

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