

Variant: *NM_000277.1(PAH):c.1183G>C (p.Ala395Pro)*

Version: 1.0

CA229373 [↗](#)

102547 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e90820bd-3677-45f6-9940-20fe8af192fa

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HGVS expressions

NM_000277.1(PAH):c.1183G>C (p.Ala395Pro)

NM_000277.1:c.1183G>C

NC_000012.12:g.102843662C>G

CM000674.2:g.102843662C>G

NC_000012.11:g.103237440C>G

CM000674.1:g.103237440C>G

NC_000012.10:g.101761570C>G

NG_008690.1:g.78941G>C

NG_008690.2:g.119749G>C

ENST00000553106.6:c.1183G>C

ENST00000307000.7:c.1168G>C

ENST00000549247.6:n.942G>C

ENST00000551114.2:n.845G>C

ENST00000553106.5:c.1183G>C

ENST00000635477.1:c.287G>C

ENST00000635528.1:n.698G>C

NM_000277.2:c.1183G>C

NM_001354304.1:c.1183G>C

NM_000277.3:c.1183G>C

NM_001354304.2:c.1183G>C

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PS3_Supporting

PP3_Strong

PM3_Strong

Evidence Links **2**

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 NM_000277.3(PAH):c.1183G>C variant is PAH is a missense variant predicted to cause substitution of alanine by proline at amino acid 395 (p.Ala395Pro). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMIDs: 9634518, 12836060). This variant has been detected in at least 5 individuals with Phenylketonuria. All individuals were compound heterozygous for the variant and distinct pathogenic variants in unknown phase (PM3_strong, PMIDs: 17502162, 12836060, 11999982, 7726156). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001017 in European (non-Finnish), which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). Mutant PAH enzyme activity showed 14-17% enzyme activity in vitro with < 10 benign/pathogenic variant controls, indicating that this variant impacts protein function (PS3_supporting, PMID: 11161839). The computational predictor REVEL gives a score of 0.988, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_moderate, PM3_strong, PM2_supporting, PS3_supporting, PP3_strong. Version 2.0, 7/16/2024.

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001017 in European (non-Finnish), which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate			At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for Phenylketonuria (PP4_Moderate, PMIDs: 9634518, 12836060). <div>PMID 9634518: excluded BH4 deficiency. In two patients, classified p.Ala395Pro as classic PKU variant. PubMed:9634518 </div>
PS3_Supporting			Mutant PAH enzyme activity 17;14 % wt (pcDNA3/IVT) and 15 +/- 7 in E.coli showed <50% enzyme activity in vitro with < 10 benign/pathogenic variant controls indicating that this variant impacts protein function (PS3_supporting, PMID: 11161839). <div>A395P mutant PAH enzyme activity 17;14 % wt (pcDNA3/IVT) and 15 +/- 7 (pET/E. coli). We have used two heterologous in vitro expression systems (cell-free rabbit reticulocyte lysates and the pET system of E. coli) to assess the residual activities and oligomeric compositions of 34 missense variants associated with PAH deficiency in the Danish and other populations. To allow direct comparisons between different mutant enzymes, our approach was designed to analyze all mutations synchronously under identical experimental conditions. Total protein concentrations were standardized to 6 mg/ml. Included negative vector control. PubMed:11161839 </div>
PP3_Strong			The computational predictor REVEL gives a score of 0.988, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM3_Strong			This variant has been detected in at least 5 individuals with Phenylketonuria. All individuals were compound heterozygous for the variant and distinct pathogenic variants in unknown phase (PM3_strong, PMIDs: 17502162, 12836060, 11999982, 7726156).

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Showing 1 to 1 of 1 rows

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