

Variant: NM_000277.2(PAH):c.581T>C (p.Leu194Pro)

Version: 1.0

CA229633 [↗](#)

102742 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 434f1539-4967-4ff7-abc2-e2ff3ca9ecbe

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HGVS expressions

NM_000277.2:c.581T>C

NM_000277.2(PAH):c.581T>C (p.Leu194Pro)

NC_000012.12:g.102855261A>G

CM000674.2:g.102855261A>G

NC_000012.11:g.103249039A>G

CM000674.1:g.103249039A>G

NC_000012.10:g.101773169A>G

NG_008690.1:g.67342T>C

NG_008690.2:g.108150T>C

NM_000277.1:c.581T>C

NM_001354304.1:c.581T>C

NM_000277.3:c.581T>C

ENST00000307000.7:c.566T>C

ENST00000549111.5:n.677T>C

ENST00000553106.5:c.581T>C

Likely Pathogenic

Met criteria codes **4**

PM3_Strong

PP4_Moderate

PP3

PM2

Evidence Links **4**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM2: Absent from 1000G, ESP. gnomAD MAF:0.00004.; PP3: Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.899; PM3_Strong: Detected in trans with V245A and R261X, both pathogenic (PMID:7981714; PMID:16601866); PP4_Moderate: Detected in 3 patients (1 HPA, 1 PKU). BH4 deficiency excluded in 2 patients. (PMID:8533759; PMID:7981714; PMID:9012412; PMID:16601866). In summary this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM2, PP3, PM3_Strong, PP4_Moderate).

Met criteria codes

PM3_Strong	✓	Detected in trans with V245A and R261X, both pathogenic Patient 28 genotype: L194P/R261X (VarID610, Path). All the mutations identified were confirmed by analysing parental DNA, which also enabled us to follow the segregation of the mutations. PubMed:16601866 Patient F: V245A (VarID632, Path) /L194P. The mutations identified were confirmed by restriction analysis of PCR products reamplified from genomic DNA in affected subjects and their parents. PubMed:7981714
PP4_Moderate	✓	Detected in 3 patients (1 HPA, 1 PKU). BH4 deficiency excluded in 2 patients. L194P detected in 2 chromosomes of PKU patients from 4 centers in Great Britain. PubMed:9012412 Patient 28 detected w/L194L (Mild PKU). A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:16601866 Likely same patient as Zschocke 1994. dihydrobiopterin reductase deficiency was excluded. HPA, 237 umol/L PubMed:8533759 Patient F had L194P. Phe levels 237 umol/L. PubMed:7981714
PP3	✓	Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.899
PM2	✓	Absent from 1000G, ESP. gnomAD MAF:0.00004.

Curation History

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