

## 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

**UID:** 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**

**PP3**

**PM2**

**PP4\_Moderate**

**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](#)

#### PP3



Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.899

#### PM2



Absent from 1000G, ESP. gnomAD MAF:0.00004.

#### 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](#)

### Curation History [↗](#)

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