The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2018-08-13
Published on: 2019-04-06

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

PP3 PM3_Strong 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

PP3	✔	Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.899
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
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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