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.731C>T (p.Pro244Leu)

Version: 1.0

CA229721

621 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 344642d3-8c14-42b5-b882-2e78163506b4
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HGVS expressions

NM_000277.2(PAH):c.731C>T (p.Pro244Leu)
NM_000277.2:c.731C>T
NC_000012.12:g.102852926G>A
CM000674.2:g.102852926G>A
NC_000012.11:g.103246704G>A
CM000674.1:g.103246704G>A
NC_000012.10:g.101770834G>A
NG_008690.1:g.69677C>T
NG_008690.2:g.110485C>T
ENST00000553106.6:c.731C>T
ENST00000307000.7:c.716C>T
ENST00000549247.6:n.490C>T
ENST00000553106.5:c.731C>T
NM_000277.1:c.731C>T
NM_001354304.1:c.731C>T
NM_000277.3:c.731C>T
NM_001354304.2:c.731C>T

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PM2 PP4_Moderate

Not Met criteria codes 2

PM5 PS3

Evidence Links 8

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.731C>T (p.Pro244Leu) variant in PAH has been reported in 2 individuals with mild PKU or benign HPA (BH4 deficiency excluded). It was detected in trans with pathogenic variants I65T, PMID: 1363838 and p.R261Q)parental analysis not reported PMID: 23430859). This variant has extremely low frequency in gnomAD (MAF= 0.00002979) and ExAC (MAF=0.00009). Computational evidence supports a

deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, Polyphen2, Mutation Taster. REVEL=0.937
PM3	✔	P244L detected in trans with I65T, pathogenic/likely pathogenic in ClinVar PMID: 1363838 detected with p.R261Q (P 9 submitters) parental analysis not reported PMID: 23430859 PubMed:16165389 PubMed:23430859 This patient had mutant haplotypes 12/9 and carried the previously described mutation I65T (VarID 636, P/LP in ClinVar) on the haplotype 9 allele. P244L was on haplotype 12, paternally inherited. PubMed:1363838
PM2	✔	Absent from 1000G, ESP. Extremely low frequency in gnomAD (MAF= 0.00002979) and ExAC (MAF=0.00009)
PP4_Moderate	✔	P244L identified in 2 Spanish PKU patients. BH4 deficiency excluded. mild PKU-PMID: 1363838 benign HPA-PMID: 23430859 PubMed:8981952 PubMed:15464430 PubMed:10234516 Sequence analysis of exon 7 of patient NL (mild PKU, Phe 720 umol/l) revealed a new single base substitution of a C to a T at the second base of codon 244, causing a substitution of a Pro (CCT) for a Leu (CTT). PubMed:1363838

Not Met criteria codes

PM5	✖	The current variant is the only variant found in this codon in ClinVar.
PS3	✖	2 in vitro studies show 67-70% activity. 51% enzyme activity per BioPKU/Dr. Blau. In this work, we use a combined approach of expression in eukaryotic cells at different temperatures and a prokaryotic system with co-expression of chaperonins to elucidate and confirm structural consequences for 18 PKU mutations. P244L had relative residual activity: 68.27%+/-11.9, 67.6% +/-25, at 37 and 27 degrees C. PubMed:12655546 Expression analysis was performed in COS cells using the human expression vector pRc/CMV. The oligonucleotide-directed mutagenesis kit from Amersham was used to introduce the P244L mutation in the PAH sequence. PAH enzymatic activity in transfected cells and in rat liver was assayed. Extracts from cells expressing the P244L mutation had 70% control activity. RNA and Western blot analysis revealed similar levels of PAH in RNA and immunoreactive protein in cells transfected with the mutant and wt PAH cDNA. PubMed:7749420

Curation History

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