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_000277.3(PAH):c.1330C>T (p.Leu444Phe)

Version: 1.0

CA386492873

551287 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 36f8536e-265a-49f1-825f-de11b9fa12b5
Approved on: 2026/1/6
Published on: 2026/1/6

HGVS expressions

NM_000277.3(PAH):c.1330C>T (p.Leu444Phe)
NM_000277.3:c.1330C>T
NC_000012.12:g.102839204G>A
CM000674.2:g.102839204G>A
NC_000012.11:g.103232982G>A
CM000674.1:g.103232982G>A
NC_000012.10:g.101757112G>A
NG_008690.1:g.83399C>T
NG_008690.2:g.124207C>T
ENST00000553106.6:c.1330C>T
ENST00000307000.7:c.1315C>T
ENST00000551114.2:n.992C>T
ENST00000553106.5:c.1330C>T
ENST00000635528.1:n.845C>T
NM_000277.1:c.1330C>T
NM_000277.2:c.1330C>T
NM_001354304.1:c.1330C>T
NM_001354304.2:c.1330C>T

Likely Pathogenic

Met criteria codes 4

PM3_Strong PP3 PP4 PM2

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1330C>T (p.Leu444Phe) variant in PAH was detected in multiple patients with PKU in trans with the pathogenic variants c.441+3G>C(PMID: 28982351) and c.722G>A (PMID: 26600521). This variant was absent in population databases. Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_Strong, PM2, PP3, PP4.

Met criteria codes

PM3_Strong	✔	This variant was detected in trans with the pathogenic variants c.441+3G>C and c.722G>A (PMID: 28982351, 26600521). points=2
PP3	✔	Predicted to be damaging (SIFT), probably damaging (PolyPhen2), Disease causing (MutationTaster). REVEL=0.885
PP4	✔	Variant was detected in 2 patients affected with PKU. Variable sites in patient genes were aligned with the corresponding sites from the respective parents. This was seen in trans with another variant listed in ClinVar. Those with BH4 cofactor deficiency were excluded PMID: 28982351, 26600521
PM2	✔	This variant is present in European (non-Finnish) populations at a frequency of 0.00006 (Gnomad). This variant is absent from the Exac population database

Not Met criteria codes

PM5	✖	No other variants have been documented in ClinVar at this amino acid residue.

Curation History

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