

Variant: *NM_000277.2(PAH):c.331C>T (p.Arg111Ter)*

Version: 1.0

CA251526 [↗](#)

581 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a0f4f502-3d14-496e-92b6-b2160d5d9013

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HGVS expressions

NM_000277.2:c.331C>T

NM_000277.2(PAH):c.331C>T (p.Arg111Ter)

NC_000012.12:g.102894756G>A

CM000674.2:g.102894756G>A

NC_000012.11:g.103288534G>A

CM000674.1:g.103288534G>A

NC_000012.10:g.101812664G>A

NG_008690.1:g.27847C>T

NG_008690.2:g.68655C>T

NM_000277.1:c.331C>T

NM_001354304.1:c.331C>T

NM_000277.3:c.331C>T

ENST00000307000.7:c.316C>T

ENST00000546844.1:c.331C>T

ENST00000548928.1:n.253C>T

ENST00000549111.5:n.427C>T

ENST00000550978.6:n.315C>T

ENST00000551337.5:c.331C>T

ENST00000551988.5:n.420C>T

ENST00000553106.5:c.331C>T

Pathogenic

The Expert Panel has overridden the computationally generated classification - "Uncertain Significance - Insufficient Evidence"

Met criteria codes **3**

PP4_Moderate

PM3_Very Strong

PVS1

Not Met criteria codes **1**

PM2

Evidence Links **5**

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: PVS1: Nonsense variant; PP4_Moderate: Seen in multiple Chinese PKU patients. BH4 deficiency excluded. (PMID:1301187; PMID:2816939; PMID:9860305); PM3_very-strong: Detected in trans with 6 known pathogenic variants: p.R158Q; p.R241C; p.R243Q; p.E280K; p.Y356*; p.R413P

(PMID:15503242, 26322415). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PVS1, PP4_Moderate, PM3_very-strong).

Met criteria codes

PP4_Moderate



Seen in multiple Chinese PKU patients. BH4 deficiency excluded.

Detected 3 times in Japanese patients with PKU. Patients with BH4 deficiency were excluded based on the absence of neurologic deterioration on a low phenylalanine diet, analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test, and/or pteridine analysis of urine. [PubMed:9860305](#)

R111X is seen in 9.1% of Chinese PKU patients associated with haplotype 4. Wang et al. 1989. [PubMed:1301187](#)

An Arg111-to-Ter111 mutation has been identified in exon 3 of the PAH gene in a Chinese PKU patient. Classic, severe PKU was confirmed by Guthrie test and clinical criteria with plasma Phe level > 20 mg/dl. 2 other PKU patients had R111Ter, and an additional 5 alleles were identified with haplotype 4, and an additional 5 patients without haplotyping data. [PubMed:2816939](#)

PM3_Very Strong



Detected with: p.R158Q (P, 11 submitters); p.R241C (P, 7 submitters); p.R243Q (P, 7 submitters); p.E280K (P, 9 submitters); p.Y356* (P, 5 submitters); p.R413P (P, 6 submitters)

Detected in 13 patients with: c.611A>G, p.E280K, p.Y356*, p.V399V, p.Y154H, p.R158Q, p.R241C, p.R243Q, p.G307D, p.A322T, p.I324N, p.R413P. All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing.

[PubMed:26322415](#)

Patient 29: R111X/R243Q (VarID591, Pathogenic) [PubMed:15503242](#)

PVS1



Nonsense variant

Not Met criteria codes

PM2



Absent from 1000G, ESP. ExAC MAF=0.00029.

[Curation History](#)

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