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.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
Approved on: 2019-04-09
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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

PM3_Very Strong PP4_Moderate 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

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
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
PVS1	✔	Nonsense variant

Not Met criteria codes

PM2	✖	Absent from 1000G, ESP. ExAC MAF=0.00029.

Curation History

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