

Variant: *NM_000277.2(PAH):c.158G>A (p.Arg53His)*

Version: 1.0

CA229447 [↗](#)

102601 (ClinVar) [↗](#)

Gene: PAH (HGNC:5053)

Condition: phenylketonuria (MONDO:0009861)

Inheritance Mode: Autosomal recessive inheritance

UID: 0b0aa28d-6844-4b34-a270-410f26ce9504

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HGVS expressions

NM_000277.2:c.158G>A

NM_000277.2(PAH):c.158G>A (p.Arg53His)

NC_000012.12:g.102912801C>T

CM000674.2:g.102912801C>T

NC_000012.11:g.103306579C>T

CM000674.1:g.103306579C>T

NC_000012.10:g.101830709C>T

NG_008690.1:g.9802G>A

NG_008690.2:g.50610G>A

NM_000277.1:c.158G>A

NM_001354304.1:c.158G>A

NM_000277.3:c.158G>A

ENST00000307000.7:c.143G>A

ENST00000546844.1:c.158G>A

ENST00000548677.2:n.245G>A

ENST00000548928.1:n.80G>A

ENST00000549111.5:n.254G>A

ENST00000550978.6:n.142G>A

ENST00000551337.5:c.158G>A

ENST00000551988.5:n.247G>A

ENST00000553106.5:c.158G>A

ENST00000635500.1:n.126G>A

Uncertain Significance

Met criteria codes **3**

PP4_Moderate BS1 PM3

Not Met criteria codes **1**

PP3

Evidence Links **2**

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: **BS1: MAF=0.01596 in ExAC (138/8648) and 0.0104 in gnomAD (265/18868 with 3 homozygotes); PP4_moderate: Detected in multiple patients with hyperphenylalaninemia, BH4 deficiency excluded (PMID:24401910, 26322415); PM3: Detected in trans with pathogenic variant p.R243Q. In summary this variant meets criteria to be classified as uncertain significance for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (BS1, PP4_moderate, PM3).**

Met criteria codes

PP4_Moderate



Detected in multiple patients with mild hyperphenylalaninemia (MHP, Phe levels<10 mg/dl), BH4 deficiency excluded.

mild hyperphe?

[PubMed:24401910](#)

c.158G>A p.R53H identified on 8 alleles. All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2 mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. [PubMed:26322415](#)

BS1



MAF=0.01596 in ExAC (138/8648) and 0.0104 in gnomAD (265/18868 with 3 homozygotes)

PM3



Detected in trans with p.R243Q (P, 7 submitters) PMID: 26322415

Compound heterozygosity with V388L (LP) [PubMed:24401910](#)

Patient genotype: c.[158G>A];[728G>A],p.[R53H];[R243Q]. 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](#)

Not Met criteria codes

PP3



Conflicting predictions of pathogenicity: Disease causing in MutationTaster, Benign in Polyphen-2 (HVAR). REVEL=0.789.

Curation History [↗](#)

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