

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

CA229447 [↗](#)

102601 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

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

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HGVS expressions

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

NM_000277.2:c.158G>A

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**

BS1

PP4_Moderate

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

BS1			MAF=0.01596 in ExAC (138/8648) and 0.0104 in gnomAD (265/18868 with 3 homozygotes)
PP4_Moderate			<div>Detected in multiple patients with mild hyperphenylalaninemia (MHP, Phe levels<10 mg/dl), BH4 deficiency excluded.</div> <div>mild hyperphe? PubMed:24401910</div> <div>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</div>
PM3			<div>Detected in trans with p.R243Q (P, 7 submitters) PMID: 26322415</div> <div>Compound heterozygosity with V388L (LP) PubMed:24401910</div> <div>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</div>

Not Met criteria codes

PP3			Conflicting predictions of pathogenicity: Disease causing in MutationTaster, Benign in Polyphen-2 (HVAR). REVEL=0.789.
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Curation History

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