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.158G>A (p.Arg53His)

Version: 1.0

CA229447

102601 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0b0aa28d-6844-4b34-a270-410f26ce9504
Approved on: 2019-04-08
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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

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	✔	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
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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