Variant: NM_000277.2(PAH):c.782G>T (p.Arg261Leu)

Version: 1.2

CA386295444

585208 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 055ab2d3-4e6f-434a-99f2-3769457ebb64
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HGVS expressions

NM_000277.2:c.782G>T
NM_000277.2(PAH):c.782G>T (p.Arg261Leu)
NC_000012.12:g.102852875C>A
CM000674.2:g.102852875C>A
NC_000012.11:g.103246653C>A
CM000674.1:g.103246653C>A
NC_000012.10:g.101770783C>A
NG_008690.1:g.69728G>T
NG_008690.2:g.110536G>T
ENST00000553106.6:c.782G>T
ENST00000307000.7:c.767G>T
ENST00000549247.6:n.541G>T
ENST00000553106.5:c.782G>T
NM_000277.1:c.782G>T
NM_001354304.1:c.782G>T
NM_000277.3:c.782G>T
NM_001354304.2:c.782G>T

Uncertain Significance

Met criteria codes 3

PP3 PM5 PM2

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.782G>T (p.Arg261Leu) variant in PAH has been previously reported Pathogenic by one clinical laboratory in ClinVar (see variant ID 576255); the laboratory stated that it was found as an “inherited” allele in 1 Han Chinese proband with PKU (subtype not otherwise specified, no further phenotypic details given). No further information regarding zygosity, familial segregation, and/or functional assays was provided, and no formal classification criteria were given, aside from “case-control” was given in the collection method. The variant results in a substitution of a highly conserved Arg residue with Leucine; the two amino acid residues are physiochemically distinct (basic

versus nonpolar side chains) and the substitution is predicted damaging by multiple lines of computational evidence, e.g., Predicted deleterious in SIFT, Polyphen2, Mutation Taster. REVEL= 0.979) (PP3). It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). [Although there is frequency data retrieved for it in the PAGE/GGV browser in the ClinGen VCI, when the genomic coordinates for it are entered into the browser, nothing comes up…]. Other missense changes at this Arg (Arg261) have been previously reported Pathogenic or Likely Pathogenic in ClinVar, e.g., p.Arg261Gln (Pathogenic per internal PAH ClinGen Working Group classification, ClinVar ID 582), as well as p.Arg261Gly and p.Arg261Pro (PM5).

Met criteria codes

PP3	✔	The variant results in a substitution of a highly conserved Arg residue with Leucine; the two amino acid residues are physiochemically distinct (basic versus nonpolar side chains) and the substitution is predicted damaging by multiple lines of computational evidence, e.g., Predicted deleterious in SIFT, Polyphen2, Mutation Taster. REVEL= 0.979) (PP3).
PM5	✔	Other missense changes at this Arg (Arg261) have been previously reported Pathogenic or Likely Pathogenic in ClinVar, e.g., p.Arg261Gln (Pathogenic per internal PAH ClinGen Working Group classification, ClinVar ID 582), as well as p.Arg261Gly and p.Arg261Pro (PM5).
PM2	✔	It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). [Although there is frequency data retrieved for it in the PAGE/GGV browser in the ClinGen VCI, when the genomic coordinates for it are entered into the browser, nothing comes up…]

Curation History

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