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

Version: 2.0

CA386295444

585208 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 055ab2d3-4e6f-434a-99f2-3769457ebb64
Approved on: 2024/11/17
Published on: 2024/11/18

HGVS expressions

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

Likely Pathogenic

Met criteria codes 3

PM5 PP3_Strong PM2_Supporting

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
Criteria Specification Approval History
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_Strong). It is absent from control databases including ethnically matched individuals, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2_Supporting). 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). In summary, this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: PM2_Supporting, PP3_Strong, PM5.

Met criteria codes

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).
PP3_Strong	✔	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). REVEL score 0.979 is over 0.929 cutoff for PP3_Strong.
PM2_Supporting	✔	It is absent from gnomAD v4.1.0

Curation History

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