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Variant: NM_000277.3:c.292T>G

Version: 1.0

CA16020761

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: cfd0acfb-d16d-459e-b078-1bcf48ce9158
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HGVS expressions

NM_000277.3:c.292T>G
NC_000012.12:g.102894795A>C
CM000674.2:g.102894795A>C
NC_000012.11:g.103288573A>C
CM000674.1:g.103288573A>C
NC_000012.10:g.101812703A>C
NG_008690.1:g.27808T>G
NG_008690.2:g.68616T>G
NM_000277.1:c.292T>G
NM_000277.2:c.292T>G
NM_001354304.1:c.292T>G
ENST00000307000.7:c.277T>G
ENST00000546844.1:c.292T>G
ENST00000548928.1:n.214T>G
ENST00000549111.5:n.388T>G
ENST00000550978.6:n.276T>G
ENST00000551337.5:c.292T>G
ENST00000551988.5:n.381T>G
ENST00000553106.5:c.292T>G

Likely Pathogenic

Met criteria codes 3

PM2 PM3 PP4_Moderate

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

The c.292T>G (p.Leu98Val) variant in PAH has been reported in multiple individuals with mild PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 26322415, 26503515). This variant is absent in population databases (PM2). This variant was detected in trans with

p.R408W (P, 16 submitters) (PM3). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.

Met criteria codes

PM2	✔	Absent from controls in ExAC/gnomAD, 1000 Genomes, or ESP
PM3	✔	detected in trans with p.R408W (P, 16 submitters) c.[292T>G];[1222C>T], p.[L98V];[R408W]. 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
PP4_Moderate	✔	c.292T>G (p.L98V) identified in a patient with mild PKU. BH4 deficiency was excluded. PMID: 26322415, PMID: 26503515 p.L98V detected on 3 alleles PubMed:26503515 c.292T>G (p.L98V) identified in a patient with mild PKU. 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

Not Met criteria codes

PP3	✖	Computational evidence is conflicting (SIFT: T,D; PolyPhen2: P,B; MutationTaster: D; REVEL=0.704)

Curation History

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