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Variant: NM_001354304.2:c.977G>C

Version: 2.0

CA16020913

1327560 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9f5f4825-ebcd-40b8-83e0-0cdfe6a937d0
Approved on: 2024/9/6
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HGVS expressions

NM_001354304.2:c.977G>C
NC_000012.12:g.102844424C>G
CM000674.2:g.102844424C>G
NC_000012.11:g.103238202C>G
CM000674.1:g.103238202C>G
NC_000012.10:g.101762332C>G
NG_008690.1:g.78179G>C
NG_008690.2:g.118987G>C
ENST00000553106.6:c.977G>C
ENST00000307000.7:c.962G>C
ENST00000549247.6:n.736G>C
ENST00000551114.2:n.639G>C
ENST00000553106.5:c.977G>C
ENST00000635477.1:c.81G>C
ENST00000635528.1:n.492G>C
NM_000277.1:c.977G>C
NM_000277.2:c.977G>C
NM_001354304.1:c.977G>C
NM_000277.3:c.977G>C

Likely Pathogenic

Met criteria codes 5

PP4 PM3_Supporting PP3_Moderate PM2_Supporting PM5_Supporting

Not Met criteria codes 1

PM1

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 NM_000277.3(PAH):c.977G>C (p.Trp326Ser) variant is a missense variant in exon 10/13 of PAH. This variant has been previously reported in at least one proband with hyperphenylalanemia (HPA; Palmieri, A. (2013). MOLECULAR ANALYSIS OF PHENYLALANINE HYDROXYLASE GENE IN SOUTH ITALY PATIENTS AFFECTED BY PHENYLKETONURIA) in whom BH4 deficiency was not formally excluded by normal urine pterins and normal DHPR activity, or sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism (PP4_Supporting). This variant has been reported in at least one proband with the genotype p.Leu48Ser/p.Trp326Ser (phase not confirmed) phenotype (PMID: 32668217); the p.Leu48Ser variant is path in ClinVar by PAH VCEP (Var ID: 608) (PM3_Supporting). The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.874) (PP3_Moderate). A different missense variant at the same site, p.Trp326Cys, has been previously reported in one patient with HPA (PMID: 36537053), BH4 deficiency not excluded, in presumed trans w/p.R408W (path by PAH VCEP, ClinVar ID 577); the p.W326C variant qualifies as likely path (PM3_Supp, PP3_Mod, PP4_Mod (hyperphenylalanemia, BH4 deficiency excluded by sequencing of genes in sequencing of genes in the BH4 cofactor metabolism pathway, PM2_Supp), such that PM5_Supporting is met. In summary, this variant meets criteria to be classified as Likely Pathogenic based on the ACMG/AMP criteria applied, as specified by the ClinGen Phenylketonuria Variant Curation Expert Panel (Specifications Version 2.0): PM2_Supporting, PM3_Supporting, PM5_Supporting, PP4_Supporting, PP3_Moderate.

Met criteria codes

PP4	✔	Previously reported in one individual with hyperphenylalanemia type II (plasma Phe 600–1200 mmol/L) in whom BH4 deficiency was not formally excluded by normal urine pterins and normal DHPR activity, or sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism. (Palmieri, A. (2013). MOLECULAR ANALYSIS OF PHENYLALANINE HYDROXYLASE GENE IN SOUTH ITALY PATIENTS AFFECTED BY PHENYLKETONURIA. http://www.fedoa.unina.it/9088/1/TESI%20DOTTORATO%20ALESSIA%20PALMIERI.pdf)
PM3_Supporting	✔	reported in 2 cases with genotype p.Leu48Ser/p.Trp326Ser, phase not confirmed, phenotype not specified. Leu48Ser is path in ClinVar by PAH VCEP (Var ID: 608), and PM3 used for the L48S variant did not include occurrences with W326S, thereby avoiding circularity. Given uncertainty if cases were related and if phase confirmed, gave this 0.5pts (for path variant in one proband w/o phase confirmed) to be conservative.
PP3_Moderate	✔	REVEL score 0.875 (between 0.773 - 0.932 range for moderate)
PM2_Supporting	✔	Not found in any population database
PM5_Supporting	✔	A different missense variant at the same site, p.Trp326Cys, has been previously reported in one patient with HPA (PMID: 36537053), BH4 deficiency not excluded, in presumed trans w/p.R408W (path by PAH VCEP, ClinVar ID 577). The p.W326C variant qualifies as likely path (PM3_Supp, PP3_Mod, PP4_Mod (hyperphenylalanemia, BH4 deficiency excluded by sequencing of genes in sequencing of genes in the BH4 cofactor metabolism pathway, PM2_Supp).

Not Met criteria codes

PM1	✖	Not in one of the designated mutational hotspots per PAH VCEP

Curation History

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