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Variant: NM_000277.3(PAH):c.561G>C (p.Trp187Cys)

Version: 1.0

CA229626

102737 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1c0ae89b-f759-4875-b648-8f454598bad8
Approved on: 2021/10/31
Published on: 2022/6/12

HGVS expressions

NM_000277.3:c.561G>C
NM_000277.3(PAH):c.561G>C (p.Trp187Cys)
NC_000012.12:g.102855281C>G
CM000674.2:g.102855281C>G
NC_000012.11:g.103249059C>G
CM000674.1:g.103249059C>G
NC_000012.10:g.101773189C>G
NG_008690.1:g.67322G>C
NG_008690.2:g.108130G>C
ENST00000553106.6:c.561G>C
ENST00000307000.7:c.546G>C
ENST00000549111.5:n.657G>C
ENST00000551988.5:n.582G>C
ENST00000553106.5:c.561G>C
NM_000277.1:c.561G>C
NM_000277.2:c.561G>C
NM_001354304.1:c.561G>C
NM_001354304.2:c.561G>C

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PM3_Supporting PP4_Moderate PM2 PP3

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.561G>C (p.Trp187Cys) variant in PAH has been reported in a Japanese PKU patient (BH4 deficiency ruled out, genotype not reported; 21307867), and 2 Brazilian siblings with PKU (PMID: 30829006). It was detected with the pathogenic variant p.Val388Met in the siblings.

PAH activity for this variant was 1% compared to wild type in a COS cell expression system (PMID: 9860305). This variant is absent in population databases, and predicted deleterious in multiple lines of computational evidence. In summary, this variant meets the criteria to be classified as Likely pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH VCEP: PP4_moderate, PS3_supporting, PM2, PM3_supporting, PP3.

Met criteria codes

PS3_Supporting	✔	PAH activity for W187C was 1% compared to wild type in COS cell expression system. PMID: 9860305 This PMID approved for PS3-supp on PAH VCEP call 2/25/22
PM3_Supporting	✔	detected with V388M (P by 6 submitters) in Brazilian siblings, parental analysis not reported PMID: 30829006. Genotype not reported for Japanese patient.
PP4_Moderate	✔	Reported in a Japanese PKU patient (analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine PMID: 21307867) and 2 Brazilian siblings with PKU (moderate and mild) PMID: 30829006
PM2	✔	absent in gnomAD
PP3	✔	Predicted deleterious in SIFT, Polyphen-2, MutationTaster, REVEL=0.94

Not Met criteria codes

PM5	✖	p.Trp187Arg is LP by PAH VCEP.

Curation History

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