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Variant: NM_000277.2(PAH):c.493G>A (p.Ala165Thr)

Version: 1.0

CA229579

102700 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 08ff348d-98b9-47fa-97c5-2f3d8fb04a8a
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HGVS expressions

NM_000277.2(PAH):c.493G>A (p.Ala165Thr)
NM_000277.2:c.493G>A
NC_000012.12:g.102866612C>T
CM000674.2:g.102866612C>T
NC_000012.11:g.103260390C>T
CM000674.1:g.103260390C>T
NC_000012.10:g.101784520C>T
NG_008690.1:g.55991G>A
NG_008690.2:g.96799G>A
NM_000277.1:c.493G>A
NM_001354304.1:c.493G>A
NM_000277.3:c.493G>A
ENST00000307000.7:c.478G>A
ENST00000549111.5:n.589G>A
ENST00000551988.5:n.530+10850G>A
ENST00000553106.5:c.493G>A

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP1 PP3 PM2 PM3

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.493G>A (p.Ala165Thr) variant in PAH has been reported in multiple individuals with PKU, including siblings (BH4 deficiency excluded). (PP4_Moderate, PMID: 8981952; PP1, PMID: 26666653). This variant has extremely low frequency in gnomAD (MAF=0.00001) (PM2). This variant was detected with c.1066-11G>A (PM3; PMID: 10598814). Multiple lines of computational evidence support a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP1, PP3.

Met criteria codes

PP4_Moderate	✔	A165T was detected in multiple patients with PKU, Bh4 deficiency excluded. PMID: 8981952 Sixty-three Spanish PKU families representing 129 independent chromosomes were included in this study. Patients were considered as having PKU when the serum phenylalanine levels at diagnosis were >600 umol/liter and after exclusion of a defect in tetrahydrobiopterine metabolism. A165T was detected on 1 allele PubMed:8981952
PP1	✔	c.493G>A;493G>A genotype was observed in two cPKU siblings PMID: 26666653 c.493G>A]; [493G>A] genotype was observed in two cPKU siblings. The one tested between 3 and 10 years of age showed no decrease in Phe concentration (H0 384 µmol/L) while the one tested in the neonatal period showed a 36% decrease (H0 1680 µmol/L) but is not currently under BH4 treatment. PubMed:26666653
PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.941)
PM2	✔	extremely low frequency in gnomAD (MAF=0.00001)
PM3	✔	detected with c.1066-11G>A (IVS10) PMID: 10598814 and in the homozygous state (PMID: 19786003) Patient 20: homozygous for p.A165T. Mendelian inheritance in parents and carrier analysis was performed by DGGE. Thus, it was possible to confirm homozygosity due to mutation inheritance from both parents and also to define the carriers. PubMed:19786003 Patient genotype: IVS10/A165T PubMed:10598814

Curation History

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