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Variant: NM_000277.2(PAH):c.796A>C (p.Thr266Pro)

CA267673

120286 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9d15f844-7f1a-47ea-91e3-fa8a96d0342c
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HGVS expressions

NM_000277.2(PAH):c.796A>C (p.Thr266Pro)
NM_000277.2:c.796A>C
NC_000012.12:g.102852861T>G
CM000674.2:g.102852861T>G
NC_000012.11:g.103246639T>G
CM000674.1:g.103246639T>G
NC_000012.10:g.101770769T>G
NG_008690.1:g.69742A>C
NG_008690.2:g.110550A>C
NM_000277.1:c.796A>C
NM_001354304.1:c.796A>C
NM_000277.3:c.796A>C
ENST00000307000.7:c.781A>C
ENST00000549247.6:n.555A>C
ENST00000553106.5:c.796A>C

Likely Pathogenic

Met criteria codes 4

PM3 PM2 PP3 PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.796A>C (p.Thr266Pro) variant in PAH is reported in 1 classic PKU patient with BH4 deficiency excluded. (PMID: 26666653, 23430918) It was detected with p.V190A, which is interpreted as pathogenic by our PAH VCEP. (PMID: 23430918) This variant is absent from ExAC, gnomAD, 1000G, and ESP. It is predicted deleterious in SIFT, Polyphen-2, MutationTaster, and REVEL=0.98. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_Moderate, PM3, PP3.

Met criteria codes

PM3	✔	Detected with V190A, Pathogenic per ClinGen Metabolic workgroup. PMID: 23430918 PAH genotype: p.V190A (VarID 102740, no clinical significance provided): p.T266P. PubMed:23430918
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.98
PP4_Moderate	✔	T266P idenitifed in 1 classic PKU patient. BH4 deficiency was excluded. PMID: 26666653, 23430918 A total of 364 French patients among which, 9 % had mild hyperphenylalaninemia, 17.7 % mild phenylketonuria and 73.1 % classical phenylketonuria had the PAH gene sequenced and analyzed by Multiplex Ligation Probe Amplification. p.Thr266P reported in 1 patient with classic PKU. Likely same patient as Sarkissian due to same reported genotype (V190A/T266P). PubMed:26666653 Prospectively enrolled phenylketonuria patients (n=485) participated in an international Phase II clinical trial to identify the prevalence of a therapeutic response to daily doses of sapropterin dihydrochloride. T266P was identified in 1 patient. Patients with a diagnosis of primary BH4 deficiency were excluded from the study. PubMed:23430918

Not Met criteria codes

PM5	✖	T266L and T266A seen before, but no clinical significance reported in ClinVar.

Curation History

Showing 1 to 1 of 1 rows

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