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Variant: NM_000277.3(PAH):c.1157A>G (p.Tyr386Cys)

Version: 1.0

CA274152

102538 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6acafcea-f40e-4329-8055-3934e23f7427
Approved on: 2021/5/15
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HGVS expressions

NM_000277.3(PAH):c.1157A>G (p.Tyr386Cys)
NM_000277.3:c.1157A>G
NC_000012.12:g.102843688T>C
CM000674.2:g.102843688T>C
NC_000012.11:g.103237466T>C
CM000674.1:g.103237466T>C
NC_000012.10:g.101761596T>C
NG_008690.1:g.78915A>G
NG_008690.2:g.119723A>G
ENST00000553106.6:c.1157A>G
ENST00000307000.7:c.1142A>G
ENST00000549247.6:n.916A>G
ENST00000551114.2:n.819A>G
ENST00000553106.5:c.1157A>G
ENST00000635477.1:c.261A>G
ENST00000635528.1:n.672A>G
NM_000277.1:c.1157A>G
NM_000277.2:c.1157A>G
NM_001354304.1:c.1157A>G
NM_001354304.2:c.1157A>G

Pathogenic

Met criteria codes 4

PM3_Very Strong | PM2 | PP4_Moderate | PP3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1157A>G (p.Tyr386Cys) variant in PAH has been reported in multiple probands with PKU (BH4 deficiency excluded) (PMID: 16198137; PP4_Moderate). This variant has been detected with c.1315+1G>A, R252W, L311P, R261Q, I65V, Q178G, R158Q (all reported as Pathogenic

in ClinVar, 4.0 points total) (PMIDs:24368688, 24941924, 22841515, 16198137, 26210745, 23357515, 18493213; PM3_very-strong). This variant is absent from population databases (PM2) and is predicted deleterious by SIFT, PolyPhen2, MutationTaster, and REVEL = 0.975 (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4_Moderate, PP3.

Met criteria codes

PM3_Very Strong	✔	Y386D detected with c.1315+1G>A, R252W, L311P, R261Q, I65V, Q178G, R158Q (all reported as Pathogenic in ClinVar, 4.0 points total) (PMIDs:24368688, 24941924, 22841515, 16198137, 26210745, 23357515, 18493213)
PM2	✔	Data is absent from population databases ExAC, 1000 Genomes, and extremely low in gnomAD and ESP (MAF=0.00004, 0.00012 respectively)
PP4_Moderate	✔	PMID: 24941924 - Y386C detected in 1 Mexican patient with classic PKU (Phe >1200umol/L), BH4 deficiency not excluded; PMID: 16198137 - Y386D detected in 1 Italian patient with classic PKU, plasma Phe >1200umol/L; BH4 deficiency excluded via BH4 loading test, analysis of urinary pterins - patients genotype (Y386D/R261Q) stated to be BH4 responsive with 31.5% reduction in plasma phe at 8 h; PMID: 18493213 - Y386C detected in 1 patient with moderate PKU, serum Phe = 10mg/dL; BH4 deficiency excluded via urinary pterin analysis
PP3	✔	Predicted deleterious by SIFT, PolyPhen2, MutationTaster, and REVEL = 0.975.

Curation History

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