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Variant: NM_000277.3(PAH):c.1130A>G (p.Tyr377Cys)

Version: 1.0

CA229357

102534 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8cfc0af2-0d67-45a5-a855-7b335c37f5f1
Approved on: 2022/3/11
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HGVS expressions

NM_000277.3(PAH):c.1130A>G (p.Tyr377Cys)
NM_000277.3:c.1130A>G
NC_000012.12:g.102843715T>C
CM000674.2:g.102843715T>C
NC_000012.11:g.103237493T>C
CM000674.1:g.103237493T>C
NC_000012.10:g.101761623T>C
NG_008690.1:g.78888A>G
NG_008690.2:g.119696A>G
ENST00000553106.6:c.1130A>G
ENST00000307000.7:c.1115A>G
ENST00000549247.6:n.889A>G
ENST00000551114.2:n.792A>G
ENST00000553106.5:c.1130A>G
ENST00000635477.1:c.234A>G
ENST00000635528.1:n.645A>G
NM_000277.1:c.1130A>G
NM_000277.2:c.1130A>G
NM_001354304.1:c.1130A>G
NM_001354304.2:c.1130A>G

Likely Pathogenic

Met criteria codes 5

PM3 PM5 PM2 PP3 PP4_Moderate

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.2(PAH):c.1130A>G (p.Tyr377Cys) variant is a missense variant in exon 11/13 of PAH. The variant has been previously reported in trans with p.R243* (Pathogenic in ClinVar and per ClinGen PAH VCEP) in a PKU patient (plasma Phe 765 umol/L); BH4 deficiency

was excluded by analysis of urinary pterins and dihydropterine reductase assays (PMID: 22526846) (PM3; PP4_Moderate). One heterozygote and zero homozygotes are present for the variant in gnomAD, corresponding to a global frequency of 0.00000398 and a maximum population frequency (non-Finnish European) of 0.00000879, under the frequency cutoff of 0.0002 for use of PM2 (PM2). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.849), so PP3 is met. PM5 also applies because a different missense variant at the same amino acid residue, p.Y377D, qualifies as Likely Pathogenic: the p.Y377D variant has been previously reported in trans with the known pathogenic c.1066-11G>A splicing mutation in a proband with PKU (plasma Phe 20-30mg/dL; BH4 formally excluded by urinary pterin and DHPR analysis) (PMID: 21890392) (PM3; PP4_Moderate), is absent in ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2), and is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.874) (PP3). Classification: Likely Pathogenic Supporting Criteria: PM2; PM3; PP4_Moderate; PM5, PP3

Met criteria codes

PM3	✔	The variant has been previously reported in trans with p.R243* (Pathogenic in ClinVar and per ClinGen PAH VCEP) in a PKU patient (plasma Phe 765 umol/L); BH4 deficiency was excluded by analysis of urinary pterins and dihydropterine reductase assays (PMID: 22526846) (PM3; PP4_Moderate).
PM5	✔	PM5 also applies because a different missense variant at the same amino acid residue, p.Y377D, qualifies as Likely Pathogenic: the p.Y377D variant has been previously reported in trans with the known pathogenic c.1066-11G>A splicing mutation in a proband with PKU (plasma Phe 20-30mg/dL; BH4 formally excluded by urinary pterin and DHPR analysis) (PMID: 21890392) (PM3; PP4_Moderate), is absent in ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2), and is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.874) (PP3).
PM2	✔	One heterozygote and zero homozygotes are present for the variant in gnomAD, corresponding to a global frequency of 0.00000398 and a maximum population frequency (non-Finnish European) of 0.00000879, under the frequency cutoff of 0.0002 for use of PM2 (PM2).
PP3	✔	SIFT predicts tolerated, other software predicts damaging. REVEL=0.849 (includes SIFT) so okay to apply PP3 per PAH VCEP.
PP4_Moderate	✔	The variant has been previously reported in trans with p.R243* (Pathogenic in ClinVar and per ClinGen PAH VCEP) in a PKU patient (plasma Phe 765 umol/L); BH4 deficiency was excluded by analysis of urinary pterins and dihydropterine reductase assays (PMID: 22526846) (PM3; PP4_Moderate).

Curation History

Showing 1 to 1 of 1 rows

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