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Variant: NM_000277.1:c.1250A>G

Version: 1.0

CA16020983

1327551 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5f01e97d-3749-408c-a4a3-0d28f3549e87
Approved on: 2020/8/13
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HGVS expressions

NM_000277.1:c.1250A>G
NC_000012.12:g.102840465T>C
CM000674.2:g.102840465T>C
NC_000012.11:g.103234243T>C
CM000674.1:g.103234243T>C
NC_000012.10:g.101758373T>C
NG_008690.1:g.82138A>G
NG_008690.2:g.122946A>G
ENST00000553106.6:c.1250A>G
ENST00000307000.7:c.1235A>G
ENST00000551114.2:n.912A>G
ENST00000553106.5:c.1250A>G
ENST00000635477.1:c.354A>G
ENST00000635528.1:n.765A>G
NM_000277.2:c.1250A>G
NM_001354304.1:c.1250A>G
NM_000277.3:c.1250A>G
NM_001354304.2:c.1250A>G

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP3 PM5 PM2 PP4_Moderate

Not Met criteria codes 1

PS3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1250A>G (p.Tyr417Cys) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 21147011). This variant has extremely low frequency in gnomAD (MAF=0.00001). It was detected with the pathogenic variant IVS10-

11G>A (PMID: 28593914). Computational evidence support a deleterious effect. Another missense change at the same amino acid (p.Tyr417His) is interpreted as pathogenic. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM5, PM3_supporting, PP3.

Met criteria codes

PM3_Supporting	✔	detected with IVS10-11G>A. parental analysis not reported PMID: 28593914
PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster, REVEL=0.95
PM5	✔	p.Tyr417His interpreted as pathogenic by 1 submitter (GeneDx) and PAH VCEP
PM2	✔	Absent from ExAC, 1000G, ESP. MAF=0.00001 in gnomAD (ENF)
PP4_Moderate	✔	Y417C seen on 4 alleles of hyperphenylalaninemic patients (blood Phe <600 µmol/L). BH4 deficiency excluded (sequencing of PAH, PTS, and QDPR genes. PMID: 21147011

Not Met criteria codes

PS3	✖	In vitro functional study showed Y417C mutant had 76% activity of wt PAH. A robust LC-ESI-MSMS PAH assay for the quantification of phenylalanine and tyrosine was developed. Compared to the wild-type enzyme, the highest PAH activity at standard conditions (1 mmol/L L-Phe; 200 µmol/L BH(4)) was found for the mutant p.Y417C (76%). PubMed:22300847

Curation History

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