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Variant: NM_000277.2(PAH):c.997C>T (p.Leu333Phe)

Version: 1.0

CA114366

624 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dfc4fff9-3ef3-4b41-ac3a-94f9f8b7aa2d
Approved on: 2022/3/13
Published on: 2022/4/16

HGVS expressions

NM_000277.2(PAH):c.997C>T (p.Leu333Phe)
NM_000277.2:c.997C>T
NC_000012.12:g.102844404G>A
CM000674.2:g.102844404G>A
NC_000012.11:g.103238182G>A
CM000674.1:g.103238182G>A
NC_000012.10:g.101762312G>A
NG_008690.1:g.78199C>T
NG_008690.2:g.119007C>T
ENST00000553106.6:c.997C>T
ENST00000307000.7:c.982C>T
ENST00000549247.6:n.756C>T
ENST00000551114.2:n.659C>T
ENST00000553106.5:c.997C>T
ENST00000635477.1:c.101C>T
ENST00000635528.1:n.512C>T
NM_000277.1:c.997C>T
NM_001354304.1:c.997C>T
NM_000277.3:c.997C>T
NM_001354304.2:c.997C>T

Pathogenic

Met criteria codes 5

PM2 PM3_Strong PS3_Supporting PP3 PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.997C>T (p.Leu333Phe) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). It was detected with multiple pathogenic variants: p.E390G (PMID: 8098245); p.R261Q (PMID: 21147011); p.S110L (LP by PAH VCEP, PMID: 26542770). This variant is absent in population databases. In an eukaryotic expression system, the L333F mutant had 7% PAH activity as compared to wild type (PMID: 10479481). Computational evidence supports a deleterious effect. In summary, this variant meets criteria to be classified as Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PP4_Moderate, PM2, PP3, PS3_supporting.

Met criteria codes

PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PM3_Strong	✔	L333F seen with E390G (Pathogenic/Likely Pathogenic), parental analysis not reported PMID: 8098245; Homozygous (PMID: 20920871); p.R261Q (P), parental analysis not routinely performed (PMID: 21147011); in trans with c.329C>T, p.S110L (LP by PAH VCEP, PMID: 26542770) 2.0 points
PS3_Supporting	✔	In an eukaryotic expression system, L333F mutant had 7% PAH activity as compared to wt. PMID: 10479481. This is consistent with in vivo measurement: A needle biopsy of the liver showed a PAH activity of 10% of the control (6 micromoles of tyr/h/g of protein). Genotype was L333F/E390G. PMID: 8098245
PP3	✔	Predicted deleterious in SIFT, Polyphen2, LRT, FATHMM, PROVEAN
PP4_Moderate	✔	Seen in 1 patient with hyperphe. Cofactor deficiency ruled out: a needle biopsy of the liver, performed to rule out a cofactor deficiency, showed a PAH activity of 10% of the control (6 micromoles of tyr/h/g of protein). Dihydropteridine reductase activity was normal (90 nanomoles/min/mg of protein). PMID: 8098245

Not Met criteria codes

PM5	✖	No other variant in this codon in ClinVar

Curation History

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