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Variant: NM_000277.3(PAH):c.329C>T (p.Ser110Leu)

Version: 1.0

CA229516

102651 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: fa22eff0-ef3f-4eef-a040-0550adb5ba5f
Approved on: 2021/12/16
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HGVS expressions

NM_000277.3(PAH):c.329C>T (p.Ser110Leu)
NM_000277.3:c.329C>T
NC_000012.12:g.102894758G>A
CM000674.2:g.102894758G>A
NC_000012.11:g.103288536G>A
CM000674.1:g.103288536G>A
NC_000012.10:g.101812666G>A
NG_008690.1:g.27845C>T
NG_008690.2:g.68653C>T
ENST00000553106.6:c.329C>T
ENST00000307000.7:c.314C>T
ENST00000546844.1:c.329C>T
ENST00000548928.1:n.251C>T
ENST00000549111.5:n.425C>T
ENST00000550978.6:c.313C>T
ENST00000551337.5:c.329C>T
ENST00000551988.5:n.418C>T
ENST00000553106.5:c.329C>T
NM_000277.1:c.329C>T
NM_000277.2:c.329C>T
NM_001354304.1:c.329C>T
NM_001354304.2:c.329C>T

Likely Pathogenic

Met criteria codes 3

PM2 PM3 PP4_Moderate

Not Met criteria codes 1

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.329C>T (p.Ser110Leu) variant in PAH has been reported in one individual with mild hyperphenylalanemia, in trans to c.842C>T (p.Pro281Leu) (Likely pathogenic by PAH VCEP variation ID: 589) with exclusion of BH4 deficiency (PMID: 16051511, PMID: 12618080). It has also been observed in an additional patient with hyperphenylalanemia without specified exclusion of BH4 deficiency (PMID: 26542770). In-vitro functional studies are unavailable. This variant is absent from population databases. In-silico predictions yield conflicting results regarding the pathogenicity of this variant. In summary, this variant meets criteria to be classified as Likely Pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3, PP4_moderate, PM2.

Met criteria codes

PM2		✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, and ESP.
PM3	ⓘ	✔	Observed with c.842C>T (p.Pro281Leu) (Likely pathogenic by PAH VCEP variation ID: 589), confirmed in trans (PMID: 16051511).
PP4_Moderate	ⓘ	✔	Observed in a patient with mild hyperphenylalanemia with plasma phe levels exceeding 240umol/L. "A defect of BH4 synthesis or regeneration was excluded by measuring dihydropteridine reductase activity in dried blood filter card samples and by determination of pterins in urine samples collected before and during BH4 loading tests." (PMID: 16051511). Also observed in a second patient with hypherphenylalanemia with Phe level 293 umol/L. Exclusion of BH4 deficiency not specified (PMID: 26542770).

Not Met criteria codes

PP3	ⓘ	✖	Tolerated and Damaging in SIFT, Probably Damaging in PP-2, Disease-causing in MutationTaster, REVEL=0.717

Curation History

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