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Variant: NM_000277.2(PAH):c.194T>A (p.Ile65Asn)

CA229479

102623 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a1719899-148c-4be8-9193-1d376d4059d9
Approved on: 2018-12-09
Published on: 2018-12-10

HGVS expressions

NM_000277.2(PAH):c.194T>A (p.Ile65Asn)
NM_000277.2:c.194T>A
NC_000012.12:g.102894893A>T
CM000674.2:g.102894893A>T
NC_000012.11:g.103288671A>T
CM000674.1:g.103288671A>T
NC_000012.10:g.101812801A>T
NG_008690.1:g.27710T>A
NG_008690.2:g.68518T>A
NM_000277.1:c.194T>A
NM_001354304.1:c.194T>A
NM_000277.3:c.194T>A
ENST00000307000.7:c.179T>A
ENST00000546844.1:c.194T>A
ENST00000548677.2:n.281T>A
ENST00000548928.1:n.116T>A
ENST00000549111.5:n.290T>A
ENST00000550978.6:n.178T>A
ENST00000551337.5:c.194T>A
ENST00000551988.5:n.283T>A
ENST00000553106.5:c.194T>A
ENST00000635500.1:n.162T>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PM3 PM2 PP3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.194T>A (p.Ile65Asn) variant was identified in a patient with classic PKU. BH4 deficiency was ruled out. (PMID: 9521426). It was detected in trans with known pathogenic mutation c.143T>C (p.L48S). It has an extremely low frequency in PAGE (0.00026); and is absent from ExAC, 1000 Genomes, gnomAD. Multiple lines of computational evidence support a deleterious effect (SIFT, Polyphen-2, MutationTaster; REVEL=0.957). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PP4_Moderate, PP3.

Met criteria codes

PP4_Moderate	✔	c.194T>A (p.I65N) was identified in a patient with classic PKU. BH4 deficiency ruled out. PMID: 9521426 c.194T>A (p.I65N) was identified in trans to the known c.143T>C (L48S) mutation in patient F18 with classic PKU. The occurrence of defects involving homeostasis or synthesis of the phenylalanine hydroxylase cofactor (BH4) was ruled out by dosing the urinary pterins. PubMed:9521426
PM3	✔	c.194T>A (p.I65N) was detected in trans with known pathogenic mutation c.143T>C (p.L48S). PMID: 9521426 c.194T>A (p.I65N) was identified in trans to the known c.143T>C (L48S) mutation in a patient with classic PKU. Segregation was tested for seven of the eight new mutations by DGGE (DG) and/or DNA sequencing(DS) and/or enzymatic digestion (ED). Parental origin of I65N could not be ascertained because the father's DNA was not available. PubMed:9521426
PM2	✔	Extremely low frequency in PAGE (0.00026); Absent from ExAC, 1000 Genomes, gnomAD.
PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, Polyphen-2, MutationTaster; REVEL=0.957).

Curation History

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