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Variant: NM_000277.2(PAH):c.194T>C (p.Ile65Thr)

CA251544

636 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 633ef5e6-95c8-4ff5-88b2-6cf22b99158b
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HGVS expressions

NM_000277.2(PAH):c.194T>C (p.Ile65Thr)
NM_000277.2:c.194T>C
NC_000012.12:g.102894893A>G
CM000674.2:g.102894893A>G
NC_000012.11:g.103288671A>G
CM000674.1:g.103288671A>G
NC_000012.10:g.101812801A>G
NG_008690.1:g.27710T>C
NG_008690.2:g.68518T>C
ENST00000553106.6:c.194T>C
ENST00000307000.7:c.179T>C
ENST00000546844.1:c.194T>C
ENST00000548677.2:n.281T>C
ENST00000548928.1:n.116T>C
ENST00000549111.5:n.290T>C
ENST00000550978.6:c.178T>C
ENST00000551337.5:c.194T>C
ENST00000551988.5:n.283T>C
ENST00000553106.5:c.194T>C
ENST00000635500.1:n.162T>C
NM_000277.1:c.194T>C
NM_001354304.1:c.194T>C
NM_000277.3:c.194T>C
NM_001354304.2:c.194T>C

Pathogenic

Met criteria codes 4

PM3_Very Strong | PP4_Moderate | PS3 | PP3

Not Met criteria codes 4

PM2 | PM5 | PS1 | PP1

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM3_VeryStrong: Detected with Y414C (P), R408W (P), P281L (P), IVS10nt-11 (P), R252W (P/LP), and R243Q(P). (PMID:12501224; PMID:1301201; PMID:10767174); PP3: Predicted dleterious in SIZFT, Polyphen2, MutationTaster. REVEL=0.985; PP4_Moderate: Detected in a patient with mild PKU. BH4 deficiency excluded. Upgraded per ClinGen PAH EP. (PMID:12501224); PS3: 25% mutant enzyme activity in COS cells as compared in wt (PMID:1301201). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM3_VeryStrong, PP3, PP4_Moderate, PS3).

Met criteria codes

PM3_Very Strong ✔

Detected with Y414C (P), R408W (P), P281L (P), IVS10nt-11 (P), R252W (P/LP), and R243Q(P).

We amplified and sequenced exon 3 from a PKU proband harboring the R408W allele on the other chromosome (see John et al., 1990, family #6). We identified a T to C transition in codon 65 (Fig. 1A). This substitution changes an isoleucine codon (ATT) to one for threonine (ACT); no other changes were found in the entire coding region or in the exon intron boundaries of the PAH gene. The I65T mutation, segregated with this haplotype in the nuclear family (Fig. 1B). PubMed:1301201
Patient 24 Genotype: I65T/Y414C PubMed:12501224
F13 and G3: I65T/P281L; G21: I65T/IVS10nt-11; G62: I65T/R252W; F38: I65T/I65T; F27: I65T/R243Q.
PubMed:10767174

PP4_Moderate ✔

Detected in a patient with mild PKU. BH4 deficiency excluded. Upgraded per ClinGen PAH EP.

38 children with various classes of hyperphenylalaninemia stratified according to the plasma phenylalanine concentration before treatment (normal, 30 to 120 µmol per liter). A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. Patient 24 had mild PKU, and I65T. PubMed:12501224

PS3 ✔

25% mutant enzyme activity in COS cells as compared in wt

expression analysis of the I65T mutation in COS cells demonstrating 75% loss of both immunoreactive protein and enzyme activity PubMed:1301201

PP3 ✔

Predicted dleterious in SIZFT, Polyphen2, MutationTaster. REVEL=0.985

Not Met criteria codes

PM2 ✖

gnomAD MAF: 0.00058

The. c.194T>C (p.I65T) variant was identified in a homozygous state in patients with hyperphenylalaninemia (HPA) in a study of 83 individuals from the Southern region of Portugal. PubMed:21871829

PM5 ✖

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 3 of 3 rows

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