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Variant: NM_000277.2(PAH):c.199T>C (p.Ser67Pro)

Version: 1.0

CA229481

102625 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 41884c41-0039-4205-b495-a83f4fcef082
Approved on: 2023/3/16
Published on: 2023/3/16

HGVS expressions

NM_000277.2(PAH):c.199T>C (p.Ser67Pro)
NM_000277.2:c.199T>C
NC_000012.12:g.102894888A>G
CM000674.2:g.102894888A>G
NC_000012.11:g.103288666A>G
CM000674.1:g.103288666A>G
NC_000012.10:g.101812796A>G
NG_008690.1:g.27715T>C
NG_008690.2:g.68523T>C
ENST00000553106.6:c.199T>C
ENST00000307000.7:c.184T>C
ENST00000546844.1:c.199T>C
ENST00000548677.2:n.286T>C
ENST00000548928.1:n.121T>C
ENST00000549111.5:n.295T>C
ENST00000550978.6:c.183T>C
ENST00000551337.5:c.199T>C
ENST00000551988.5:n.288T>C
ENST00000553106.5:c.199T>C
ENST00000635500.1:n.167T>C
NM_000277.1:c.199T>C
NM_001354304.1:c.199T>C
NM_000277.3:c.199T>C
NM_001354304.2:c.199T>C

Pathogenic

Met criteria codes 4

PM2 PM3_Very Strong PP3 PP4_Moderate

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.199T>C (p.Ser67Pro) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded). (PP4_Moderate; 8533759; 26351554). This variant has an extremely low allele frequency in ExAC (MAF=0.00002, PM2). This variant was detected in trans with L48S (PMID: 8592329), IVS10-11G>A, R408Q (P), R261Q, R252W (P/LP) PMID: 26351554 (PM3_VS). Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster, REVEL=0.954) (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_VS, PM2, PP4_Moderate, PP3.

Met criteria codes

PM2	✔	Extremely low frequency in ExAC (MAF=0.00002)
PM3_Very Strong	✔	Detected in trans with: L48S (PMID: 8592329, parental testing performed), IVS10-11G>A, R408Q (P), R261Q, R252W (P/LP) (PMID: 26351554, parental testing performed). p.R408W(c.1222C>T) (3 patients), p.R252W(c.754C>T) (2 patients) parental testing not reported PMID: 24350308 A total of 218 alleles from109 individuals from 40 PKU families (40 PKU patients and their parents) were tested for S67P. Observed mutations in the patients were inherited from their parents. s67p/s67p; 2 patients, s67p/ivs10nt-11: 7 patients; s67p/r261q: 3 patients; r408q/s67p: 1 patient; s67p/r252w: 1 patient. PubMed:26351554 Patient III-4 genotype: L48S (maternal)/S67P (paternal). L48S: VarID608, Pathogenic. PubMed:8592329
PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster, REVEL=0.954)
PP4_Moderate	✔	S67P was detected in 1 PKU patient. DHPR deficiency was excluded. PMID: 8533759 A total of 121 Northern Irish families with HPA (111 with PKU and 10 with MHP) were investigated. Dihydrobiopterin reductase deficiency was excluded. S67P was detected on 1 allele. PubMed:8533759

Curation History

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