

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

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HGVS expressions

NM_000277.2:c.199T>C

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

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**

PM3_Very Strong

PP4_Moderate

PP3

PM2

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**

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

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 			
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 			
PP3			Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen-2, MutationTaster, REVEL=0.954)
PM2			Extremely low frequency in ExAC (MAF=0.00002)

Curation History



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