

Variant: *NM_000277.3(PAH):c.205C>T (p.Pro69Ser)*

Version: 1.0

CA229486 [↗](#)

102628 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 9370fcab-fbf4-4a22-a254-33daee7a31c0

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HGVS expressions

NM_000277.3(PAH):c.205C>T (p.Pro69Ser)

NM_000277.3:c.205C>T

NC_000012.12:g.102894882G>A

CM000674.2:g.102894882G>A

NC_000012.11:g.103288660G>A

CM000674.1:g.103288660G>A

NC_000012.10:g.101812790G>A

NG_008690.1:g.27721C>T

NG_008690.2:g.68529C>T

ENST00000553106.6:c.205C>T

ENST00000307000.7:c.190C>T

ENST00000546844.1:c.205C>T

ENST00000548677.2:n.292C>T

ENST00000548928.1:n.127C>T

ENST00000549111.5:n.301C>T

ENST00000550978.6:c.189C>T

ENST00000551337.5:c.205C>T

ENST00000551988.5:n.294C>T

ENST00000553106.5:c.205C>T

ENST00000635500.1:n.173C>T

NM_000277.1:c.205C>T

NM_000277.2:c.205C>T

NM_001354304.1:c.205C>T

NM_001354304.2:c.205C>T

Likely Pathogenic

Met criteria codes **3**

PP4_Moderate

PM2

PM3

Not Met criteria codes **5**

PP3

PM1

PM5

PS1

PS3

Evidence Links **0**

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.205C>T (p.Pro69Ser) variant in PAH has been reported in at least two individuals with PKU without specified Phe levels, including at least one for whom BH4 deficiency has been excluded (PMID: 15503242, PMID: 32668217, PMID: 26503515). p.Pro69Ser has been detected at least twice with p.Arg261Gln, which is classified pathogenic by PAH VCEP, but without documentation of parental testing to establish phase. In-vitro studies show reduced enzyme activity, but not below the PAH VCEP cutoff of 50% (PMID: 16253218). p.Pro69Ser is absent from population databases. Multiple lines of computational evidence yield inconsistent predictions regarding the impact of this substitution. In summary, this variant meets criteria to be classified as likely pathogenic. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.

Met criteria codes

PP4_Moderate			Observed with PAH deficiency with BH4 deficiency excluded, but without a documented Phe level and without a known PKU type (PMID: 15503242, PMID: 26503515).
PM2			Absent from 1000G, ESP, gnomAD
PM3			P69S observed at least twice with R261Q, which is pathogenic according to PAH VCEP (ID 582)

Not Met criteria codes

PP3			Computational predictions yield inconsistent results (predicted tolerated in SIFT, possibly damaging in Polyphen2, disease-causing in MutationTaster, REVEL = 0.673).
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No additional variants at this codon in ClinVar.
PS1			No additional variants at this codon in ClinVar.
PS3			Kim et al. 2006 PMID: 16253218 – in-vitro expression analysis showed mean enzyme activity 52% of wild-type (PS3 not met)

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