

Variant: *NM_000277.3(PAH):c.208T>C (p.Ser70Pro)*

Version: 1.0

CA229488 [↗](#)

102631 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 12dc078f-4f90-4e29-a304-abfd5153cb71

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HGVS expressions

NM_000277.3:c.208T>C

NM_000277.3(PAH):c.208T>C (p.Ser70Pro)

NC_000012.12:g.102894879A>G

CM000674.2:g.102894879A>G

NC_000012.11:g.103288657A>G

CM000674.1:g.103288657A>G

NC_000012.10:g.101812787A>G

NG_008690.1:g.27724T>C

NG_008690.2:g.68532T>C

ENST00000553106.6:c.208T>C

ENST00000307000.7:c.193T>C

ENST00000546844.1:c.208T>C

ENST00000548677.2:n.295T>C

ENST00000548928.1:n.130T>C

ENST00000549111.5:n.304T>C

ENST00000550978.6:c.192T>C

ENST00000551337.5:c.208T>C

ENST00000551988.5:n.297T>C

ENST00000553106.5:c.208T>C

ENST00000635500.1:n.176T>C

NM_000277.1:c.208T>C

NM_000277.2:c.208T>C

NM_001354304.1:c.208T>C

NM_001354304.2:c.208T>C

Likely Pathogenic

Met criteria codes **5**

PP3

PS3_Supporting

PM2

PM3_Supporting

PP4_Moderate

Not Met criteria codes **2**

PP1

PM5

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Phenylketonuria VCEP

The c.208T>C (p.Ser70Pro) variant in PAH has been reported in at least four individuals with hyperphenylalanemia, including at least one for whom BH4 deficiency was excluded (PMID: 9860305, PMID: 21307867). Of these, two were siblings who also had p.Arg241His (PMID: 22330942), which is classified as pathogenic by PAH VCEP (Variation ID: 102804), without documentation of parental testing to establish phase. In-vitro studies show 20% enzyme activity (PMID: 9860305). This variant is absent from population databases. Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP3, PP4, PM2, PM3_Supporting, PS3_supporting.

Met criteria codes

PP3			Damaging in SIFT, probably damaging in PP-2, disease-causing in MutationTaster, REVEL=0.968
PS3_Supporting			Okano et al. 1998 PMID: 9860305 – in vitro PAH activity of mutant PAH cDNA construct in a COS cell expression system showed mean enzyme activity 20% of wild-type. PS3_supp approved for use for this PMID on PAH VCEP call 2/25/22.
PM2			Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PM3_Supporting			Two sibs with p.Ser70Pro and p.Arg241His (classified as Path by PAH VCEP, Variation ID: 102804). However, phase undescribed. Per SVI guidelines "If the phase cannot be determined, it is recommended that at least two different LP/P variants (depending on classifications) are needed to equal the weight of one LP/P co-occurrence confirmed in trans." Only one LP/P variant in this case, as these are two related individuals, so this situation reflects 0.5 points for one (phase unknown) occurrence of Ser70Pro with Arg241His.
PP4_Moderate			p.Ser70Pro observed in association with PAH deficiency with BH4 deficiency excluded, but without documented plasma phenylalanine levels (PMID: 9860305, PMID: 21307867). Plasma Phe levels >120 umol/L without documentation of exclusion of BH4 deficiency (PMID: 22330942).

Not Met criteria codes

PP1			Two affected segregations and no unaffected segregations noted. However, parental testing for phase not discussed (PMID: 22330942).
PM5			c.209C>T(p.Ser70Phe) classified as likely pathogenic by PAH VCEP (Variation ID: 987767). PM5 not met as p.Ser70Phe is likely path and not path.

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