

Variant: *NM\_000277.3(PAH):c.198A>G (p.Glu66=)*

Version: 1.0

CA6748999 [↗](#)

760907 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** f076b187-abf8-4e12-8f6f-27e219cd9858

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### *HGVS expressions*

**NM\_000277.3:c.198A>G**

**NM\_000277.3(PAH):c.198A>G (p.Glu66=)**

NC\_000012.12:g.102894889T>C

CM000674.2:g.102894889T>C

NC\_000012.11:g.103288667T>C

CM000674.1:g.103288667T>C

NC\_000012.10:g.101812797T>C

NG\_008690.1:g.27714A>G

NG\_008690.2:g.68522A>G

ENST00000553106.6:c.198A>G

ENST00000307000.7:c.183A>G

ENST00000546844.1:c.198A>G

ENST00000548677.2:n.285A>G

ENST00000548928.1:n.120A>G

ENST00000549111.5:n.294A>G

ENST00000550978.6:c.182A>G

ENST00000551337.5:c.198A>G

ENST00000551988.5:n.287A>G

ENST00000553106.5:c.198A>G

ENST00000635500.1:n.166A>G

NM\_000277.1:c.198A>G

NM\_000277.2:c.198A>G

NM\_001354304.1:c.198A>G

NM\_001354304.2:c.198A>G

Uncertain Significance

Met criteria codes **1**

PM2\_Supporting

Not Met criteria codes **1**

BP7

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

*Phenylketonuria VCEP*

The NM\_000277.3:c.198A>G variant in PAH is a synonymous (silent) variant (p.Glu66=) that is not predicted to impact splicing. To our knowledge, this variant has not been reported in the literature and results of functional studies are unavailable. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002641 (3/113600 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PAH VCEP’s threshold for PM2\_Supporting (<0.0002), meeting this criterion (PM2\_Supporting). There is a ClinVar entry for this variant (Variation ID: 760907, 1 star review status) with one submitter classifying the variant as a variant of uncertain significance and one submitter classifying the variant as likely benign. In summary, this variant meets the criteria to be classified as a variant of uncertain significance for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel (Specifications Version 2.0): PM2\_Supporting.

Met criteria codes

|                       |                                                                                   |                                                                                   |                                                                                                                                                                                                                                                                       |
|-----------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PM2_Supporting</b> |  |  | The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002641 (3/113600 alleles) in the European (non-Finnish) population, which is lower than the ClinGen PAH VCEP’s threshold for PM2_Supporting (<0.0002), meeting this criterion (PM2_Supporting). |
|-----------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Not Met criteria codes

|            |                                                                                    |                                                                                   |                                                                                                                                           |
|------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| <b>BP7</b> |  |  | synonymous (silent) variant (p.Glu66=) that is not predicted to impact splicing but nucleotide is conserved from humans through zebrafish |
|------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|

Curation History 



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