

Variant: *NM\_000277.1:c.47\_48dup*

Version: 1.0

CA16020717 [↗](#)

2682165 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 7db8ceb1-259a-4876-bd1f-5dcff1666777

**Approved on:** 2023/10/15

**Published on:** 2023/10/15

## HGVS expressions

### NM\_000277.1:c.47\_48dup

NC\_000012.12:g.102917087\_102917088dup

CM000674.2:g.102917087\_102917088dup

NC\_000012.11:g.103310865\_103310866dup

CM000674.1:g.103310865\_103310866dup

NC\_000012.10:g.101834995\_101834996dup

NG\_008690.1:g.5519\_5520dup

NG\_008690.2:g.46327\_46328dup

ENST00000553106.6:c.47\_48dup

ENST00000307000.7:c.-101\_-100dup

ENST00000546844.1:c.47\_48dup

ENST00000547319.1:n.358\_359dup

ENST00000549111.5:n.143\_144dup

ENST00000550978.6:c.31\_32dup

ENST00000551337.5:c.47\_48dup

ENST00000551988.5:n.136\_137dup

ENST00000553106.5:c.47\_48dup

ENST00000635500.1:n.29-4186\_29-4185dup

NM\_000277.2:c.47\_48dup

NM\_001354304.1:c.47\_48dup

NM\_000277.3:c.47\_48dup

NM\_001354304.2:c.47\_48dup

**Pathogenic**

Met criteria codes **3**

PVS1

PP4\_Moderate

PM2\_Supporting

Evidence Links **1**

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.47\_48dup (p.Asp17LeufsTer22) variant in PAH is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 1/13 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). This variant is reported on 3 alleles of patients with phenylketonuria, with BH4 deficiency excluded (PP4\_moderate, PMID: 21147011). This variant is absent from gnomAD v2.1.1 (PM2\_Supporting). In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH VCEP: PVS1, PP4\_moderate, PM2\_supporting. (Phenylketonuria VCEP specifications version 1).

Met criteria codes

|                                                                                                                                                                                                                      |                                                                                   |                                                                                   |                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| PVS1                                                                                                                                                                                                                 |  |  | Frameshift variant in exon 1 predicted to undergo NMD                                                                            |
| PP4_Moderate                                                                                                                                                                                                         |  |  | c.48_49insCT seen in 3 PKU alleles. BH4 deficiency excluded (PTS and QDPR analyzed). Upgraded per ClinGen PAH EP. PMID: 21147011 |
| 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). c.48_49insCT seen in 3 alleles. <a href="#">PubMed:21147011</a> |                                                                                   |                                                                                   |                                                                                                                                  |
| PM2_Supporting                                                                                                                                                                                                       |  |  | absent from ExAC, gnomAD v2.1.1, 1000G, ESP                                                                                      |

Curation History



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