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# *Variant: NM_000277.3(PAH):c.1117G>A (p.Ala373Thr)*

Version: 1.0

*CA229351*

*102529 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 8686a349-d7cd-48e5-8286-1fc2466ab98c
**Approved on**: 2022/6/12
**Published on**: 2022/6/12

## *HGVS expressions*

**NM_000277.3:c.1117G>A**
**NM_000277.3(PAH):c.1117G>A (p.Ala373Thr)**
NC_000012.12:g.102843728C>T
CM000674.2:g.102843728C>T
NC_000012.11:g.103237506C>T
CM000674.1:g.103237506C>T
NC_000012.10:g.101761636C>T
NG_008690.1:g.78875G>A
NG_008690.2:g.119683G>A
ENST00000553106.6:c.1117G>A
ENST00000307000.7:c.1102G>A
ENST00000549247.6:n.876G>A
ENST00000551114.2:n.779G>A
ENST00000553106.5:c.1117G>A
ENST00000635477.1:c.221G>A
ENST00000635528.1:n.632G>A
NM_000277.1:c.1117G>A
NM_000277.2:c.1117G>A
NM_001354304.1:c.1117G>A
NM_001354304.2:c.1117G>A

**Likely Pathogenic**

**Met criteria codes** 3

PM3 PM2 PP4_Moderate

**Not Met criteria codes** 3

PP3 PM5 PS3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.1117G>A (p.Ala373Thr) variant in PAH has been reported in multiple individuals with mild HPA (BH4 deficiency excluded, PP4_Moderate). This variant is absent in population databases (PM2). This variant was detected with pathogenic variants c.442-1G>A (PMID: 10484807) and in trans with p.Arg261Gln (PMID: 29316886). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3** | ✔ | detected with IVS4-1G>A. parental analysis not reported PMID: 10484807; detected in trans with p.Arg261Gln (P, 9 submitters) PMID: 29316886 |
| **PM2** | ✔ | Absent from controls in ExAC, gnomAD, 1000 Genomes, ESP |
| **PP4_Moderate** | ✔ | detected in a patient with mild HPA (4 mg/dL). BH4 deficiency excluded by urinary pteridine HPLC and DHPR activity. PMID: 10484807 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✖ | Computational evidence is conflicting: Deleterious in SIFT, MutationTaster; Benign in PolyPhen2-HVAR, REVEL=0.739. |
| **PM5** | ✖ | A373D Likely pathogenic |
| **PS3** | ✖ | Residual activity in prokaryotic system (56%) PMID: 16091306 |

Residual activity in prokaryotic system (56%); Hill coefficient 1.8; binding affinity for L-Phe of PAH mutant protein (144+/- 14) PubMed:16091306

Curation History

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