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# *Variant: NM_000277.3(PAH):c.439C>T (p.Pro147Ser)*

Version: 1.0

*CA229541*

*102669 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** e9f34e4e-66a8-4bb8-bb23-91567aa6569a
**Approved on**: 2020/10/15
**Published on**: 2020/10/15

## *HGVS expressions*

**NM_000277.3:c.439C>T**
**NM_000277.3(PAH):c.439C>T (p.Pro147Ser)**
NC_000012.12:g.102877464G>A
CM000674.2:g.102877464G>A
NC_000012.11:g.103271242G>A
CM000674.1:g.103271242G>A
NC_000012.10:g.101795372G>A
NG_008690.1:g.45139C>T
NG_008690.2:g.85947C>T
ENST00000553106.6:c.439C>T
ENST00000307000.7:c.424C>T
ENST00000549111.5:n.535C>T
ENST00000550978.6:c.423C>T
ENST00000551988.5:n.528C>T
ENST00000553106.5:c.439C>T
NM_000277.1:c.439C>T
NM_000277.2:c.439C>T
NM_001354304.1:c.439C>T
NM_001354304.2:c.439C>T

**Likely Pathogenic**

**Met criteria codes** 4

PM2 PM3_Strong PP3 PP4_Moderate

**Not Met criteria codes** 1

PM5

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**This c.439C>T (p.Pro147Ser) variant in PAH was reported in at least 5 patients with PAH deficiency, detected with pathogenic variants p.Arg243Gln (PMID: 27121329), p.S349P (PMID: 15589814), c.1045T>C, c.782G>A (PMID: 24941924) and p.A403V (PMID: 10234516). DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia (PMID: 27121329). This variant is present at an extremely low frequency in gnomAD (MAF=0.00003). Computational evidence for this missense variant supports a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PP4_moderate, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2** | ✔ | PM2_met: Extremely low frequency in gnomAD (MAF=0.00003) |
| **PM3_Strong** | ✔ | PM3_strong: This variant was detected in trans with pathogenic variants in 4 classic PKU patients and 1 mild hyperphenylalaninemia (MHP) patient (PMID: 27121329, 15589814, 24941924, 10234516). 27121329 - This variant was detected in trans with the pathogenic PAH variant p.Arg243Gln in 1 patient with classic phenylketonuria, and parental analysis was performed to confirm compound heterozygosity. 15589814 - This variant was detected in trans with the pathogenic variant S349P in 1 patient with classic phenylketonuria. Parental analysis was not performed to confirm compound heterozygosity. 24941924 - This variant was detected in trans with the pathogenic PAH variant c.1045T>C (7 pathogenic submissions in ClinVar, 1 likely pathogenic) in 1 patient with classic phenylketonuria. This variant was also detected in trans with the pathogenic PAH variant c.782G>A in 1 patient with classic phenylketonuria. Familial segregation analysis was confirmed in most patients, but it was unclear whether segregation analysis was performed for these patients. 10234516 - This variant was detected in trans with the pathogenic PAH variant A403V in at least 1 patient with mild hyperphenylalanemia (MHP). Mendelian inheritance was confirmed when parental samples were available by DGGE or restriction enzyme digestion, but it is unclear whether parental analysis was performed to confirm compound heterozygosity in this case.<br>PubMed:24941924 PubMed:10234516 PubMed:15589814 |
| **PP3** | ✔ | PP3_met: predicted deleterious in SIFT, Polyphen2, mutationTaster, REVEL=0.96 |
| **PP4_Moderate** | ✔ | PP4_moderate: Detected in a patient with classical PKU. A defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity. PMID: 27121329<br>PubMed:27121329 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | PM5_not met: P147L is interpreted as LP by PAH VCEP/ClinVar |

Curation History

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