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# *Variant: NM_000277.2(PAH):c.293T>C (p.Leu98Ser)*

*CA114368*

*627 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** fcf34e9b-443b-490c-af8d-a6643cc7dc59
**Approved on**: 2018-12-10
**Published on**: 2018-12-10

## *HGVS expressions*

**NM_000277.2(PAH):c.293T>C (p.Leu98Ser)**
**NM_000277.2:c.293T>C**
NC_000012.12:g.102894794A>G
CM000674.2:g.102894794A>G
NC_000012.11:g.103288572A>G
CM000674.1:g.103288572A>G
NC_000012.10:g.101812702A>G
NG_008690.1:g.27809T>C
NG_008690.2:g.68617T>C
ENST00000553106.6:c.293T>C
ENST00000307000.7:c.278T>C
ENST00000546844.1:c.293T>C
ENST00000548928.1:n.215T>C
ENST00000549111.5:n.389T>C
ENST00000550978.6:n.277T>C
ENST00000551337.5:c.293T>C
ENST00000551988.5:n.382T>C
ENST00000553106.5:c.293T>C
NM_000277.1:c.293T>C
NM_001354304.1:c.293T>C
NM_000277.3:c.293T>C
NM_001354304.2:c.293T>C
NM_000277.3(PAH):c.293T>C (p.Leu98Ser)

**Likely Pathogenic**

**Met criteria codes** 4

PM2 PP4_Moderate PP3 PM3_Supporting

**Not Met criteria codes** 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.293T>C (p.Leu98Ser) variant in PAH has been reported as homozygous in a Pakistani patient with mild PKU (BH4 deficiency excluded) (PMID: 8364546, 9634518, 26542770) This variant has an extremely low frequency in gnomAD v2.1.1 (MAF=0.0001307). A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and REVEL=0.846. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_supporting, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2** | ✔ | Absent from 1000G, ESP. Extremely low frequency in ExAC, gnomAD v2.1.1 (0.0001307) |
| **PP4_Moderate** | ✔ | Detected in a Pakistani patient with non-PKU hyperphenylalaninemia. BH4 deficiency excluded. ( PMID: 8364546, 9634518) Upgraded per ClinGen PAH EP. |
| **PP3** | ✔ | Deleterious effect predicted in SIFT, Polyphen-2, MutationTaster. REVEL=0.846. |
| **PM3_Supporting** | ✔ | Detected as homozygous, confirmed by parental testing PMID: 26542770 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | L98V is LP by PAH VCEP |

Curation History

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