

*Variant: NM\_000277.1(PAH):c.898G>T (p.Ala300Ser)*

CA273108 [↗](#)

92751 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 1cd06d79-1c2c-4338-936e-15faf0063222

**Approved on:** 2018-08-10

**Published on:** 2018-12-10

### *HGVS expressions*

**NM\_000277.1:c.898G>T**

**NM\_000277.1(PAH):c.898G>T (p.Ala300Ser)**

NC\_000012.12:g.102851701C>A

CM000674.2:g.102851701C>A

NC\_000012.11:g.103245479C>A

CM000674.1:g.103245479C>A

NC\_000012.10:g.101769609C>A

NG\_008690.1:g.70902G>T

NG\_008690.2:g.111710G>T

NM\_000277.2:c.898G>T

NM\_001354304.1:c.898G>T

NM\_000277.3:c.898G>T

ENST00000307000.7:c.883G>T

ENST00000549247.6:n.657G>T

ENST00000551114.2:n.560G>T

ENST00000553106.5:c.898G>T

ENST00000635477.1:n.59G>T

**Pathogenic**

**Met criteria codes** **4**

PP4\_Moderate

PM3\_Very Strong

PP3

PS3

**Not Met criteria codes** **2**

PM2

PM5

**Evidence Links** **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

#### ***Phenylketonuria VCEP***

**PAH-specific ACMG/AMP criteria applied:** PP3: Deleterious in SIFT, Polyphen2, MutationTaster; PP4\_Moderate: A300S found on 56/588 hyperphenylalaninemic patients, BH4 deficiency excluded. Upgraded per ClinGen Metabolic WG. (PMID:21147011); PM3\_VeryStrong: Detected with c.1066-11G>A (P), R261Q(P/LP), L48S (P), R176X (P) in 20 patients. (PMID:21147011); PS3: A300S in vitro PAH activity of

**31% (PMID:17935162). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PP3, PP4\_Moderate, PM3\_VeryStrong, PS3).**

Met criteria codes

|                 |                                                                                   |                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP4_Moderate    |  |  | A300S found on 56/588 hyperphenylalaninemic patients, BH4 deficiency excluded. Upgraded per ClinGen Metabolic WG.                                                                                                                                                                                                                                                                                 |
|                 |                                                                                   |                                                                                   | A total of 588 hyperphenylalaninemic patients were investigated. Assessment of the PAH gene and genes of the BH4 synthesis/ recycling pathways (PTS and QDPR). A300S found on 56 alleles. <a href="#">PubMed:21147011</a>                                                                                      |
| PM3_Very Strong |  |  | Detected with c.1066-11G>A (P), R261Q(P/LP), L48S (P), R176X (P) in 20 patients.                                                                                                                                                                                                                                                                                                                  |
|                 |                                                                                   |                                                                                   | A300S in trans with c.1066-11G>A (VarID 607, Pathogenic in ClinVar) in 10 patients. Homozygous in 9 patients. Detected with p.R261Q in 6 patients. With IVS7+4A>G in 2 patients. with p.L48S in 2 patients. with p.R176X in 2 patients. with 8 other mutations in 8 patients. <a href="#">PubMed:21147011</a>  |
| PP3             |  |  | Deleterious in SIFT, Polyphen2, MutationTaster                                                                                                                                                                                                                                                                                                                                                    |
| PS3             |                                                                                   |  | A300S in vitro PAH activity of 31%                                                                                                                                                                                                                                                                                                                                                                |
|                 |                                                                                   |                                                                                   | A300S has average residual PAH activity of 31%. <a href="#">PubMed:17935162</a>                                                                                                                                                                                                                                |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                            |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| PM2 |                                                                                     |  | MAF in gnomAD: 0.00661                                                                                                     |
| PM5 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |

Curation History 

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