

Variant: *NM_000277.1(PAH):c.898G>T (p.Ala300Ser)*

Version: 1.0

CA273108 [↗](#)

92751 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UID: 1cd06d79-1c2c-4338-936e-15faf0063222

Approved on: 2018-08-10

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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**

PM3_Very Strong **PP3** **PS3**

PP4_Moderate

Not Met criteria codes **2**

PM5 **PM2**

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

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. PubMed:21147011
PP3	✓	Deleterious in SIFT, Polyphen2, MutationTaster
PS3	✓	A300S in vitro PAH activity of 31% A300S has average residual PAH activity of 31%. PubMed:17935162
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. PubMed:21147011

Not Met criteria codes

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

Curation History [↗](#)

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