The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.899C>T (p.Ala300Val)

Version: 1.0

CA229839

102887 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 90e51a8f-6187-4d33-8f40-716b763371db
Approved on: 2020/9/24
Published on: 2022/2/11

HGVS expressions

NM_000277.1:c.899C>T
NM_000277.1(PAH):c.899C>T (p.Ala300Val)
NC_000012.12:g.102851700G>A
CM000674.2:g.102851700G>A
NC_000012.11:g.103245478G>A
CM000674.1:g.103245478G>A
NC_000012.10:g.101769608G>A
NG_008690.1:g.70903C>T
NG_008690.2:g.111711C>T
ENST00000553106.6:c.899C>T
ENST00000307000.7:c.884C>T
ENST00000549247.6:n.658C>T
ENST00000551114.2:n.561C>T
ENST00000553106.5:c.899C>T
ENST00000635477.1:c.60C>T
NM_000277.2:c.899C>T
NM_001354304.1:c.899C>T
NM_000277.3:c.899C>T
NM_001354304.2:c.899C>T

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM5 PM2

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.899C>T (p.Ala300Val) variant in PAH has been reported in at least 1 individual with PKU, detected in trans with pathogenic variant p.R408W (PMID: 8533759). This variant is absent in population databases. Computational evidence support a deleterious effect. Another

missense variant at the same amino acid (p.A300S) is pathogenic. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PM5, PP3, PP4.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster, REVEL=0.988
PP4	✔	A300V found in 1 patient with moderately severe PKU. One patient with dihydrobiopterin reductase deficiency was excluded. PMID: 8533759
		A total of 121 Northern Irish families with HPA (111 with PKU and 10 with MHP) were investigated. A300V was found in 1 patient with moderately severe PKU. PubMed:8533759
PM3	✔	A300V in trans with R408W (Pathogenic in ClinVar) The exact inheritance of mutations and STR alleles was determined in each family. PMID: 8533759
		A300V found in trans with R408W (VarID 577) Pathogenic In ClinVar. The exact inheritance of mutations and STR alleles was determined in each family. PubMed:8533759
PM5	✔	A300S (VarID 92751) is pathogenic in ClinVar (4 submitters, no conflicts)
PM2	✔	Absent from ExAC, gnomAD,1000G, ESP

Curation History

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