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_000277.2(PAH):c.1196T>C (p.Val399Ala)

Version: 1.0

CA267634

120263 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0f8fc0da-8e7b-42a0-afc5-e7d1dbc480d9
Approved on: 2020/7/10
Published on: 2020/7/10

HGVS expressions

NM_000277.2:c.1196T>C
NM_000277.2(PAH):c.1196T>C (p.Val399Ala)
NC_000012.12:g.102843649A>G
CM000674.2:g.102843649A>G
NC_000012.11:g.103237427A>G
CM000674.1:g.103237427A>G
NC_000012.10:g.101761557A>G
NG_008690.1:g.78954T>C
NG_008690.2:g.119762T>C
ENST00000553106.6:c.1196T>C
ENST00000307000.7:c.1181T>C
ENST00000549247.6:n.955T>C
ENST00000551114.2:n.858T>C
ENST00000553106.5:c.1196T>C
ENST00000635477.1:c.300T>C
ENST00000635528.1:n.711T>C
NM_000277.1:c.1196T>C
NM_001354304.1:c.1196T>C
NM_000277.3:c.1196T>C
NM_001354304.2:c.1196T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PM3_Strong PP4_Moderate

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1196T>C (p.Val399Ala) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded) detected with pathogenic variants P281L, E178G PMID: 21147011, p.R408W PMID: 23062575, c.1066-11G>A PMID: 26666653, parental analysis not

performed. This variant is absent in population databases. Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster
PM2	✔	Absent from controls in ExAC, gnomAD, 1000G, ESP
PM3_Strong	✔	V399A detected with P281L (P) and E178G (P) PMID: 21147011 p.R408W (P 14 submitters) PMID: 23062575 c.1066-11G>A (P 7 submitters) PMID: 26666653 Parental analysis not performed. V399A detected with P281L in 1 patient and p.E178G in another patient. PubMed:21147011 PubMed:26666653 PubMed:23062575
PP4_Moderate	✔	V399A found in 5 patients. BH4 deficiency excluded. Upgraded per ClinGen Metabolic WG PubMed:31332730 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). V399A found on 2 alleles. PubMed:21147011

Curation History

Showing 1 to 1 of 1 rows

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