

Variant: *NM_000277.1:c.1243G>T*

Version: 1.0

CA16020978 [↗](#)

1327547 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e80bed8c-0fdd-40df-a155-3f2773450203

Approved on: 2021/10/10

Published on: 2021/10/10

HGVS expressions

NM_000277.1:c.1243G>T
NC_000012.12:g.102840472C>A
CM000674.2:g.102840472C>A
NC_000012.11:g.103234250C>A
CM000674.1:g.103234250C>A
NC_000012.10:g.101758380C>A
NG_008690.1:g.82131G>T
NG_008690.2:g.122939G>T
ENST00000553106.6:c.1243G>T
ENST00000307000.7:c.1228G>T
ENST00000551114.2:n.905G>T
ENST00000553106.5:c.1243G>T
ENST00000635477.1:c.347G>T
ENST00000635528.1:n.758G>T
NM_000277.2:c.1243G>T
NM_001354304.1:c.1243G>T
NM_000277.3:c.1243G>T
NM_001354304.2:c.1243G>T

Pathogenic

Met criteria codes **5**

PM3_Strong

PP4_Moderate

PP3

PM2

PM5

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1243G>T (p.Asp415Tyr) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 21462123, 26503515). This variant is absent in population databases. This variant was detected in trans with pathogenic variants: p.Val399= (PMID: 28982351); and p.Ala345Thr (LP by PAH VCEP, PMID: 30050108). Computational evidence support a deleterious effect. Another missense change at the same amino acid (p.Asp415Asn) is interpreted as pathogenic by multiple submitters. In summary, this

variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_Strong, PM5, PP3.

Met criteria codes			
PM3_Strong			detected in trans with p.Val399= (P 5 submitters) variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 28982351 and p.A345T (LP by PAH VCEP/ US by 1 submitter) validation tests on parents were performed using Sanger sequencing PMID: 30050108 2.0 points
PP4_Moderate			D415Y found in 1 PKU patient. BH4 deficiency was assessed with dihydropteridine reductase activity, urinary biopterin and neopterin ratio. PMID: 21462123, 26503515 Mutations of the PAH gene were detected in exons 1-13 with flanking introns of PAH gene by PCR and DNA sequencing in 47 families with PKU. D415Y has not been reported previously. PubMed:21462123  A total of 796 unrelated patients from 29 separate newborn screening centres of China were enrolled. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading were collected. D415Y was found on 1 allele PubMed:26503515 
PP3			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster, REVEL=0.923
PM2			Absent from ExAC, gnomAD, 1000G, ESP
PM5			c.1243G>A (p.Asp415Asn) Pathogenic 9 submitters (PAH VCEP) and LP 2 submitters

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.