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:c.1123C>G

Version: 1.0

CA6748741

660581 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: ba88029d-8764-4060-8a8f-aab28ad4e29b
Approved on: 2020/6/22
Published on: 2021/9/19

HGVS expressions

NM_000277.1:c.1123C>G
NC_000012.12:g.102843722G>C
CM000674.2:g.102843722G>C
NC_000012.11:g.103237500G>C
CM000674.1:g.103237500G>C
NC_000012.10:g.101761630G>C
NG_008690.1:g.78881C>G
NG_008690.2:g.119689C>G
ENST00000553106.6:c.1123C>G
ENST00000307000.7:c.1108C>G
ENST00000549247.6:n.882C>G
ENST00000551114.2:n.785C>G
ENST00000553106.5:c.1123C>G
ENST00000635477.1:c.227C>G
ENST00000635528.1:n.638C>G
NM_000277.2:c.1123C>G
NM_001354304.1:c.1123C>G
NM_000277.3:c.1123C>G
NM_001354304.2:c.1123C>G

Likely Pathogenic

Met criteria codes 2

PM3_Very Strong | PP4_Moderate

Not Met criteria codes 3

PP3 | PM2 | PM5

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1123C>G (p.Gln375Glu) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID:26503515). It was detected in trans with pathogenic variants: p.Arg243Gln; p.Arg408Trp; EX6-96A□G (PMID: 28982351); c.977G>A

(p.W326*); p.R413P (PMID: 3005010). This variant has an allele frequency in gnomAD (MAF=0.0003808) that is above the PAH VCEP cutoff for pathogenicity (0.0002). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM3_very-strong.

Met criteria codes

PM3_Very Strong	✔	Detected with p.Arg243Gln (P 11 submitters); p.Arg408Trp (P 17 submitters); EX6-96A□G (P 6 submitters); variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 28982351; c.977G>A (p.W326*) (P 1 submitter); p.R413P (P 6 submitters) The validation tests on parents were performed using Sanger sequencing. PMID: 30050108 5.0 pts
PP4_Moderate	✔	Seen in 2 individuals with Classic PKU. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PMID: 26503515
		Seen in 2 individuals with Classic PKU. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515

Not Met criteria codes

PP3	✖	Tolerated by SIFT, deleterious by MutationTaster and PolyPhen.
PM2	✖	Seen in low frequency: gnomAD (MAF=0.0003808)
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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