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.608G>A (p.Cys203Tyr)

Version: 1.0

CA229645

102754 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d185bd34-75a8-44c2-9501-c63388a8eae4
Approved on: 2020/2/23
Published on: 2021/6/9

HGVS expressions

NM_000277.2(PAH):c.608G>A (p.Cys203Tyr)
NM_000277.2:c.608G>A
NC_000012.12:g.102855234C>T
CM000674.2:g.102855234C>T
NC_000012.11:g.103249012C>T
CM000674.1:g.103249012C>T
NC_000012.10:g.101773142C>T
NG_008690.1:g.67369G>A
NG_008690.2:g.108177G>A
ENST00000553106.6:c.608G>A
ENST00000307000.7:c.593G>A
ENST00000549111.5:n.704G>A
ENST00000553106.5:c.608G>A
NM_000277.1:c.608G>A
NM_001354304.1:c.608G>A
NM_000277.3:c.608G>A
NM_001354304.2:c.608G>A

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PM3_Strong PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.608G>A (p.Cys203Tyr) variant in PAH has been reported in 3 individuals with mild PKU and HPA (BH4 deficiency excluded). (PMID: 27121329, 23842451). This variant is absent in population databases. This variant was detected with pathogenic variants p.A300S in 2 patients (once confirmed in trans PMID: 23352389, 23500595, 27121329) and p.L348V PMID: 23842451 (2.0 points). Computational

evidence supports 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, Polyphen-2, MutationTaster, REVEL=0.98
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, and ESP
PM3_Strong	✔	Detected with p.A300S in 2 patients (P 10 submitters) PMID: 23352389, PMID: 23500595 p.L348V (P 7 submitters) PMID: 23842451 parental analysis not reported Detected in trans with p.A300S PMID: 27121329 2.0 points
PP4_Moderate	✔	Detected in Spanish and Dutch PKU patients with BH4 deficiency ruled out PMID: 27121329, PMID: 23842451

Not Met criteria codes

PM5	✖	c.609C>G p.(Cys203Trp) is LP

Curation History

Showing 1 to 1 of 1 rows

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