

Variant: *NM_001354304.2:c.223G>C*

Version: 1.0

CA386304179 [↗](#)

987769 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d632cdc3-d490-472b-be54-f09c36ae92c2

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HGVS expressions

NM_001354304.2:c.223G>C

NC_000012.12:g.102894864C>G

CM000674.2:g.102894864C>G

NC_000012.11:g.103288642C>G

CM000674.1:g.103288642C>G

NC_000012.10:g.101812772C>G

NG_008690.1:g.27739G>C

NG_008690.2:g.68547G>C

ENST00000553106.6:c.223G>C

ENST00000307000.7:c.208G>C

ENST00000546844.1:c.223G>C

ENST00000548677.2:n.310G>C

ENST00000548928.1:n.145G>C

ENST00000549111.5:n.319G>C

ENST00000550978.6:c.207G>C

ENST00000551337.5:c.223G>C

ENST00000551988.5:n.312G>C

ENST00000553106.5:c.223G>C

NM_000277.1:c.223G>C

NM_000277.2:c.223G>C

NM_001354304.1:c.223G>C

NM_000277.3:c.223G>C

Likely Pathogenic

Met criteria codes **3**

PP4_Moderate

PM2

PM3

Not Met criteria codes **2**

PP3

PM5

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.223G>C (p.Asp75His) variant in PAH was reported in 2 patients with PAH deficiency (PMID: 29499199, 28982351) detected with the pathogenic variant p.Val399= (PMID: 28982351). DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia (PMID: 29499199). This variant is absent in population databases. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PP4_moderate, PM3.

Met criteria codes

PP4_Moderate			PP4_moderate: This variant was documented 1 time in a patient with PAH deficiency (PMID: 29499199). 29499199, Wang - This variant was documented 1 time in a Chinese patient with mild hyperphenylalaninemia (MHP). All patients with the maximum pretreatment blood Phe concentrations above 120 μmol/L were enrolled. In addition, urinary pterin analysis using high performance liquid chromatography and a DHPR activity assay on DBS samples were also carried out to distinguish between PAH deficiency and tetrahydrobiopterin deficiency.
PubMed:29499199  PubMed:28982351 			
PM2			PM2_met: This variant is absent from population databases gnomAD and ExAC.
PM3			PM3_met: This variant was detected in trans with a pathogenic variant in 1 mild hyperphenylalaninemia (MHP) patient (PMID: 28982351). 28982351, Liu - This variant was detected in trans with the pathogenic PAH variant p.Val399= in 1 patient with mild hyperphenylalaninemia (MHP). Parental analysis was performed to confirm compound heterozygosity (Peripheral blood samples were collected from the patients and parents in each of the 643 core families; To determine sequence variability, variable sites in patient genes were aligned with the corresponding sites from the respective parents).

Not Met criteria codes

PP3			PP3_not met: Predicted to be tolerated (SIFT), possibly damaging (PolyPhen2), disease causing (MutationTaster). REVEL=0.645
PM5			PM5_not met: 3 other missense variants at this residue in ClinVar: p.Asp75Gly LP by PAH EP (expert panel), p.Asp75Val LP by PAH EP, p.Asp75Asn LP by 1 submitter.

Curation History 

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