

Variant: *NM_001354304.2:c.605C>T*

Version: 1.0

CA16020828 [↗](#)

1327548 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 4d996dcb-608c-4a78-aeca-572fe351e15a

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HGVS expressions

NM_001354304.2:c.605C>T

NC_000012.12:g.102855237G>A

CM000674.2:g.102855237G>A

NC_000012.11:g.103249015G>A

CM000674.1:g.103249015G>A

NC_000012.10:g.101773145G>A

NG_008690.1:g.67366C>T

NG_008690.2:g.108174C>T

ENST00000553106.6:c.605C>T

ENST00000307000.7:c.590C>T

ENST00000549111.5:n.701C>T

ENST00000553106.5:c.605C>T

NM_000277.1:c.605C>T

NM_000277.2:c.605C>T

NM_001354304.1:c.605C>T

NM_000277.3:c.605C>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM2

PM3

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.605C>T (p.A202V) variant in PAH has been reported without confirmed phase with p.Arg408Gln, which is classified as pathogenic by the PAH VCEP (Variation ID 612). It has also been observed in trans to c.442-1G>A (classified as pathogenic by PAH VCEP Variation ID 594) in a patient with classic PKU (PMID: 15319459). In-vitro functional studies are unavailable. This variant is absent from 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: PM2, PM3, PP3, PP4_moderate.

Met criteria codes

PP4_Moderate			Observed once in a population of patients with Phe levels >0.18 mM (but without a case-specific Phe level), and with BH4 deficiency excluded either through analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine (PMID 21307867). Also observed in a patient with classical PKU with serum phenylalanine concentration of greater than or equal to 1.2 mM (PMID: 15319459). After discussion at PAH VCEP meeting 11/12/21, determined that PP4_moderate can be applied despite wording of exclusion of BH4 deficiencies via biopterin loading test and/OR pteridine analysis.
PP3			Damaging in SIFT, Probably damaging in PolyPhen 2, Disease causing in MutationTaster, REVEL=0.965
PM2			Absent from controls in ExAC, gnomAD, 1000 Genomes, and ESP
PM3			Observed with p.Arg408Gln (classified as pathogenic by PAH VCEP Variation ID 612) in a patient with BH4-responsive PKU without specification of confirmed phase (PMID: 27173423). Observed in trans to c.442-1G>A (classified as pathogenic by PAH VCEP Variation ID 594) in a patient with classical PKU (PMID: 15319459).

Curation History

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