

Variant: *NM_000277.1(PAH):c.665A>T (p.Asp222Val)*

Version: 1.0

CA229681 [↗](#)

102776 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 2d746606-6991-490e-a6d3-9263659f37b8

Approved on: 2020/8/17

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HGVS expressions

NM_000277.1(PAH):c.665A>T (p.Asp222Val)

NM_000277.1:c.665A>T

NC_000012.12:g.102855177T>A

CM000674.2:g.102855177T>A

NC_000012.11:g.103248955T>A

CM000674.1:g.103248955T>A

NC_000012.10:g.101773085T>A

NG_008690.1:g.67426A>T

NG_008690.2:g.108234A>T

ENST00000553106.6:c.665A>T

ENST00000307000.7:c.650A>T

ENST00000549111.5:n.761A>T

ENST00000553106.5:c.665A>T

NM_000277.2:c.665A>T

NM_001354304.1:c.665A>T

NM_000277.3:c.665A>T

NM_001354304.2:c.665A>T

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM2

PM3

Not Met criteria codes **1**

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.665A>T (p.Asp222Val) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 21147011, 9012412). This variant is absent in population databases. This variant was detected with pathogenic variants p.R243X and p.R241H (PMID: 21147011). 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: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP4_Moderate			D222V was found in 3 PKU patients. BH4 cofactor deficiency assessed in 2 patients by analysis of PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 21147011, PMID: 9012412 PKU patients from four centers in three countries of Great Britain were studied. D222V was seen in 1 patient from Southwestern England. PubMed:9012412 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). p.D222V found on 2 alleles in 2 patients. PubMed:21147011
PP3			Predicted deleterious in SIFT, Polyphen2, and MutationTaster, REVEL=0.938
PM2			Absent from ExAC, gnomAD, 1000G, ESP
PM3			D222V found with p.R243X and p.R241H, both Pathogenic in ClinVar. parental analysis not reported PMID: 21147011 D222V found in trans with p.R243X (VarID R243X, Pathogenic) in patient with classic PKU, and p.R241H (VarID 102804, Pathogenic) in another patient with mHPA. PubMed:21147011

Not Met criteria codes

PM5			p.Asp222Gly (VarID 102775) clinical significance not provided
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Curation History

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