

Variant: *NM_000277.1(PAH):c.665A>G (p.Asp222Gly)*

Version: 1.0

CA229679 [↗](#)

102775 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c66e7bd4-9577-4574-a507-e80644413b0d

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HGVS expressions

NM_000277.1(PAH):c.665A>G (p.Asp222Gly)

NM_000277.1:c.665A>G

NC_000012.12:g.102855177T>C

CM000674.2:g.102855177T>C

NC_000012.11:g.103248955T>C

CM000674.1:g.103248955T>C

NC_000012.10:g.101773085T>C

NG_008690.1:g.67426A>G

NG_008690.2:g.108234A>G

ENST00000553106.6:c.665A>G

ENST00000307000.7:c.650A>G

ENST00000549111.5:n.761A>G

ENST00000553106.5:c.665A>G

NM_000277.2:c.665A>G

NM_001354304.1:c.665A>G

NM_000277.3:c.665A>G

NM_001354304.2:c.665A>G

Likely Pathogenic

Met criteria codes **3**

PM3_Strong

PP4_Moderate

PM2

Not Met criteria codes **2**

PP3

PM5

Evidence Links **6**

Expert Panel

[Phenylketonuria VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.665A>G (p.Asp222Gly) variant in PAH has been reported in multiple individuals with PAH deficiency (PMID: 24510552, 9429153); One had BH4 cofactor deficiency excluded (PMID: 15589814). This variant is absent in population databases. This variant was detected with multiple pathogenic variants: p.A104D (PMID: 9429153); p.R408W (PMID: 15589814); c.1066-11G>A (PMID: 23842451); p.L48S (PMID:

25757997); p.I65T (PMID: 16165389). 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, PM2, PM3_strong.

Met criteria codes

PM3_Strong			<p>D222G found with A104D parental analysis not performed (PMID: 9429153); R408W parental analysis not reported (PMID: 15589814); c.1066-11G>A parental analysis not reported (PMID: 23842451); L48S parental analysis not reported (PMID: 25757997); p.I65T parental analysis not reported (PMID: 16165389); p.S16* validation tests on parents were performed (All Pathogenic in ClinVar) 3.5 pts</p> <p>1 PKU patient had genotype c.1066-11G>A1/p.D222G PubMed:23842451 </p> <p>D222G found in trans with R408W (VarID 577, pathogenic in ClinVar) in 1 PKU patient PubMed:15589814 </p> <p>D222G found in trans with A104D (VarID 102650, Pathogenic in ClinVar) in 1 PKU patient. PubMed:9429153 </p> <p>Subject 8 had mild PKU and genotype L48S/D222G PubMed:25757997 </p>
PP4_Moderate			<p>D222G found on 3 PKU patients (PMID: 24510552, PMID: 9429153). One had BH4 cofactor deficiency excluded (PMID: 15589814).</p> <p>1 PKU patient had genotype c.1066-11G>A1/p.D222G PubMed:23842451 </p> <p>64 patients with phenylketonuria. Inclusion criteria for patients were as follows: (a) known mutations in the PAH gene or mutations in the course of investigation and pterin profile and dihydropteridine reductase activity excluding a primary defect in BH4 metabolism. Patient 27 had moderate PKU (Phe levels on unrestricted nutrition 600-1200 umol/L and tolerance: 350–400 mg Phe/day), and D222G/R408W. PubMed:15589814 </p> <p>Patient 14.1 Identified on neonatal screening. Phe at diagnosis was 950, variant PKU (plasma Phe 1200–600 uM). Genotype D222G/IVS10-11G > A. PubMed:12409276 </p> <p>GenomicDNA was isolated from total blood of 34 MHP and eight mild PKU probands from unrelated Polish families. D222G was found in 1 patient with borderline mild PKU (serum Phe 545 umol/l pretreatment, 121-605 on diet). PubMed:9429153 </p> <p>For 35 PKU children patients and 50 healthy individuals, all exons and promoters of the PAH gene were analyzed with PCR and direct sequencing. D222G was found in PKU patient. PubMed:24510552 </p>
PM2			<p>Absent in ExAC, gnomAD, 1000G, ESP</p>

Not Met criteria codes

PP3			<p>Predicted deleterious in SIFT and MutationTaster, predicted benign in Polyphen2</p>
PM5			<p>p.Asp222Val (varID 102776) clinical significance not provided in ClinVar</p>

Curation History 

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