

Variant: *NM_000277.3(PAH):c.664_665del (p.Glu221_Asp222insTer)*

Version: 1.0

CA229678 [↗](#)

133249 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 22feea98-54e8-427c-94e7-977588fb89aa

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HGVS expressions

NM_000277.3:c.664_665del

NM_000277.3(PAH):c.664_665del (p.Glu221_Asp222insTer)

NC_000012.12:g.102855178_102855179del

CM000674.2:g.102855178_102855179del

NC_000012.11:g.103248956_103248957del

CM000674.1:g.103248956_103248957del

NC_000012.10:g.101773086_101773087del

NG_008690.1:g.67425_67426del

NG_008690.2:g.108233_108234del

ENST00000553106.6:c.664_665del

ENST00000307000.7:c.649_650del

ENST00000549111.5:n.760_761del

ENST00000553106.5:c.664_665del

NM_000277.1:c.664_665del

NM_000277.2:c.664_665del

NM_001354304.1:c.664_665del

NM_001354304.2:c.664_665del

Pathogenic

Met criteria codes **4**

PP4_Moderate

PM3_Supporting

PVS1

PM2_Supporting

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen PAH Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1*

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.664_665del (p.Asp222Ter) variant in PAH is a nonsense variant in exon 6 of 13, with nonsense mediated decay predicted to occur (PVS1). This variant was detected in at least one patient with mild PKU where BH4 deficiency was excluded by analysis of neopterin and biopterin in urine and measurement of dihydropteridine reductase activity in dried blood spots (PMID:16290003, PP4_moderate). It was found to co-occur (phase unknown) with the pathogenic variant IVS10-3C>T (PM3_supporting). This deletion has a MAF of 0.00003874 in the European (non-Finnish) population in GnomAD v2.1.1 (PM2_supporting). Therefore this variant is classified as Pathogenic by the PAH VCEP; PAH-specific ACMG/AMP criteria applied: PVS1, PP4_moderate, PM2_supporting, PM3_supporting.

Met criteria codes

PP4_Moderate			Detected in a patient with mild PKU; BH4 deficiency excluded by analysis of neopterin and biopterin in urine and measurement of dihydropteridine reductase activity in dried blood spots.
PM3_Supporting			Found to co-occur with IVS10-3C>T, established pathogenic mutation in ClinVar and in ClinGen panel. The methods in the paper are vague, unclear how they established that the variants are on different alleles, lowered to supporting
PVS1			Nonsense variant in exon 6/13. NMD is predicted to occur as this is upstream of the last 50 base-pairs of the penultimate exon. Variant is in biologically relevant transcript: ENSG00000171759.9_17 from Genotype-Tissue Expression Project, GTEx database.
PM2_Supporting			MAF 0.00003874 in the European (non-Finnish) population in GnomAD v2.1.1 (shuffled variant: 12-103248954-ATC-A)

Curation History

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