

Variant: *NM_000277.1(PAH):c.715G>A (p.Gly239Ser)*

Version: 1.0

CA229706 [↗](#)

102797 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e84bc878-ccba-4772-8c4c-81be78117db9

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HGVS expressions

NM_000277.1:c.715G>A

NM_000277.1(PAH):c.715G>A (p.Gly239Ser)

NC_000012.12:g.102852942C>T

CM000674.2:g.102852942C>T

NC_000012.11:g.103246720C>T

CM000674.1:g.103246720C>T

NC_000012.10:g.101770850C>T

NG_008690.1:g.69661G>A

NG_008690.2:g.110469G>A

ENST00000553106.6:c.715G>A

ENST00000307000.7:c.700G>A

ENST00000549247.6:n.474G>A

ENST00000553106.5:c.715G>A

NM_000277.2:c.715G>A

NM_001354304.1:c.715G>A

NM_000277.3:c.715G>A

NM_001354304.2:c.715G>A

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PP3_Strong

PM3

PM5

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0

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

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.715G>A variant in PAH is a missense variant predicted to cause substitution of glycine by serine at amino acid 239 (p.Gly239Ser). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND normal urine pterins and normal DHPR activity excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 7833954, 9634518, 15503242, 26210745). Of those individuals, four were compound heterozygous for the variant and distinct pathogenic or likely pathogenic variants [unknown phase] (1.75 PM3 points). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.959, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Another missense variant c.716G>A (p.Gly239Asp) [ClinVar Variation ID: 102798] in the same codon has been classified as pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5). In summary, this variant meets criteria to be classified as pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel: PP4_Moderate, PM2_supporting, PM3, PM5, PP3_strong (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate			PMID 7833954 G239S/IVS12nt1 in a French patient with typical PKU. PMID: 9634518 exclusion of a defect in tetrahydrobiopterin metabolism PMID: 15503242 reported in a Korean patient with classical PKU. Urinary pterin analysis and dihydropteridine reductase (DHPR) assay were performed to exclude 6-pyruvoyltetrahydropterin synthase (PTPS) deficiencies.
Table 1. G239S/IVS12nt1 in a patient with typical PKU PubMed:7833954 			
PP3_Strong			The computational predictor REVEL gives a score of 0.959, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM3			1.75 points: PMID 7833954 G239S/IVS12nt1 in a patient with typical PKU DNA from parents was not available. detected with P281L (LP PAH VCEP), phasing not confirmed. PMID: 15503242 p.I65V c.193A>G (P PAH VCEP), p.R176Q c.527G>A (P PAH VCEP) parental analysis not reported PMID: 26210745
Table 1. G239S/IVS12nt1 in a patient with typical PKU PubMed:7833954 			
PM5			Another missense variant c.716G>A (p.Gly239Asp) [ClinVar Variation ID: 102798] in the same codon has been classified as pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5).

Curation History 

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