The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1(PAH):c.716G>A (p.Gly239Asp)

Version: 1.0

CA229707

102798 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: da3f74a6-7bfc-4899-8d98-a2722a49cff5
Approved on: 2025/8/15
Published on: 2025/8/15

HGVS expressions

NM_000277.1:c.716G>A
NM_000277.1(PAH):c.716G>A (p.Gly239Asp)
NC_000012.12:g.102852941C>T
CM000674.2:g.102852941C>T
NC_000012.11:g.103246719C>T
CM000674.1:g.103246719C>T
NC_000012.10:g.101770849C>T
NG_008690.1:g.69662G>A
NG_008690.2:g.110470G>A
ENST00000553106.6:c.716G>A
ENST00000307000.7:c.701G>A
ENST00000549247.6:n.475G>A
ENST00000553106.5:c.716G>A
NM_000277.2:c.716G>A
NM_001354304.1:c.716G>A
NM_000277.3:c.716G>A
NM_001354304.2:c.716G>A

Pathogenic

Met criteria codes 4

PM2_Supporting PP3_Strong PP4_Moderate PM3_Strong

Not Met criteria codes 1

PM5

Evidence Links 2

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 NM_000277.3(PAH):c.716G>A variant is PAH is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 239 (p.Gly239Asp). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) and showed defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PP4_moderate; PMID 26503515;PMID: 16256386; PMID 12905706; PMID:23932990). This variant has been detected in at least 4 individuals. Of those individuals, 3 were compound heterozygous for the variant and distinct pathogenic (2)/likely pathogenic (1) variant (V399V, R241C, p.R241Pfs*100) and 3 of those were confirmed in trans by parental analysis and sanger sequencing (PM3_strong, PMID: 16256386; PMID: 30050108). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.982, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2_supporting, PM3_strong, PP4_Moderate, PP3_strong. Version 2.0, 7/16/2024.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.982, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PP4_Moderate	✔	At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) and showed defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes (PP4_moderate; PMID 26503515;PMID: 16256386; PMID 12905706; PMID:23932990). Ten novel mutations were first time identified in Chinese PKU population as I65T, S70del, G239D, R241fsdelG, L255S, P281L, G346R, L367fsinsC, R400S and Ivsllnt2t-->c. PubMed:12905706 Reported in Table 1 The spectrum of PAH mutations in Chinese Mainland PKU patients. PubMed:26503515
PM3_Strong	✔	This variant has been detected in at least 4 individuals. Of those individuals, 3 were compound heterozygous for the variant and distinct pathogenic (2)/likely pathogenic (1) variant (V399V, R241C, p.R241Pfs*100) and 3 of those were confirmed in trans by parental analysis and sanger sequencing (PM3_strong, PMID: 16256386; PMID: 30050108).

Not Met criteria codes

PM5	✖	G239V uncertain significance. S/A no interpretation

Curation History

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