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_000277.2(PAH):c.181A>G (p.Asn61Asp)

Version: 1.0

CA229470

102617 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7dd2b63c-450a-4270-bf25-412535e6065c
Approved on: 2025/7/18
Published on: 2025/7/18

HGVS expressions

NM_000277.2(PAH):c.181A>G (p.Asn61Asp)
NM_000277.2:c.181A>G
NC_000012.12:g.102894906T>C
CM000674.2:g.102894906T>C
NC_000012.11:g.103288684T>C
CM000674.1:g.103288684T>C
NC_000012.10:g.101812814T>C
NG_008690.1:g.27697A>G
NG_008690.2:g.68505A>G
ENST00000553106.6:c.181A>G
ENST00000307000.7:c.166A>G
ENST00000546844.1:c.181A>G
ENST00000548677.2:n.268A>G
ENST00000548928.1:n.103A>G
ENST00000549111.5:n.277A>G
ENST00000550978.6:c.165A>G
ENST00000551337.5:c.181A>G
ENST00000551988.5:n.270A>G
ENST00000553106.5:c.181A>G
ENST00000635500.1:n.149A>G
NM_000277.1:c.181A>G
NM_001354304.1:c.181A>G
NM_000277.3:c.181A>G
NM_001354304.2:c.181A>G

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PP4_Moderate PM2_Supporting PM5 PP3

Evidence Links 0

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.181A>G variant in PAH is a missense variant predicted to cause substitution of asparagine to aspartic acid at amino acid 61 (p.Asn61Asp). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for Phenylketonuria (PMID:12501224) (PP4_Moderate). This individual was compound heterozygous for the variant and a pathogenic variant p.R261Q in unknown phase (PMID: 12501224, PM3_Supporting). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.703, which is above the threshold of 0.644 but below 0.773, evidence that correlates with supporting impact to PAH function (PP3). 2 different missense variants c.182A>G (p.Asn61Ser) and c.183C>A (p.Asn61Lys) in the same codon have been classified as pathogenic/likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Phenylketonuria VCEP: PP4_moderate, PP3, PM2_supporting, PM3_supporting, PM5 (Version 2.0, 7/16/2024).

Met criteria codes

PM3_Supporting	✔	This variant has been detected in at least 1 individual with Phenylketonuria. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic variant p.R261Q (PMID: 12501224, PM3_Supporting).
PP4_Moderate	✔	At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) AND sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism, which is highly specific for Phenylketonuria (PMID:12501224) (PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting)
PM5	✔	2 difference missense variant c.182A>G (p.Asn61Ser) & c.183C>A (p.Asn61Lys) in the same codon has been classified as pathogenic/likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5).
PP3	✔	The computational predictor REVEL gives a score of 0.703, which is above the threshold of 0.644 but below 0.773, evidence that correlates with supporting impact to PAH function (PP3).

Curation History

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