

Variant: *NM_000277.1:c.512G>A*

Version: 1.0

CA16020809 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9ded6bce-1853-4671-8b51-6b4f3600c485

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HGVS expressions

NM_000277.1:c.512G>A

NC_000012.12:g.102855330C>T

CM000674.2:g.102855330C>T

NC_000012.11:g.103249108C>T

CM000674.1:g.103249108C>T

NC_000012.10:g.101773238C>T

NG_008690.1:g.67273G>A

NG_008690.2:g.108081G>A

ENST00000553106.6:c.512G>A

ENST00000307000.7:c.497G>A

ENST00000549111.5:n.608G>A

ENST00000551988.5:n.533G>A

ENST00000553106.5:c.512G>A

NM_000277.2:c.512G>A

NM_001354304.1:c.512G>A

NM_000277.3:c.512G>A

NM_001354304.2:c.512G>A

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PM5_Supporting

PP3_Moderate

PM2_Supporting

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 c.512G>A variant in PAH is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid 171 (p.Gly171Glu). 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 excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 26575882, 31332730). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.926, which is above the threshold of 0.773 but below 0.932, evidence that correlates with moderate impact to PAH function (PP3_Moderate). Another missense variant c.512G>C (p.Gly171Ala) [ClinVar Variation ID: 102717] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting). In summary, this variant meets criteria to be classified as likely 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, PP3_moderate, PM5_supporting (PAH VCEP specifications version 2.0.0; approved July 16, 2024).

Met criteria codes

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 excluded a defect of BH4 cofactor metabolism, which is highly specific for PAH deficiency (PP4_Moderate, PMID: 26575882, 31332730).
PM5_Supporting			Another missense variant c.512G>C (p.Gly171Ala) [ClinVar Variation ID: 102717] in the same codon has been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.926, which is above the threshold of 0.773 but below 0.932, evidence that correlates with moderate impact to PAH function (PP3_Moderate).
PM2_Supporting			This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Curation History

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