

Variant: *NM_000277.2(PAH):c.1A>G (p.Met1Val)*

Version: 1.0

CA114360 [↗](#)

586 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UID: 89f04437-ed5d-4735-8c4a-a9b1d91d10ea

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HGVS expressions

NM_000277.2:c.1A>G

NM_000277.2(PAH):c.1A>G (p.Met1Val)

NC_000012.12:g.102917130T>C

CM000674.2:g.102917130T>C

NC_000012.11:g.103310908T>C

CM000674.1:g.103310908T>C

NC_000012.10:g.101835038T>C

NG_008690.1:g.5473A>G

NG_008690.2:g.46281A>G

NM_000277.1:c.1A>G

NM_001354304.1:c.1A>G

NM_000277.3:c.1A>G

ENST00000307000.7:c.-147A>G

ENST00000546844.1:c.1A>G

ENST00000547319.1:n.312A>G

ENST00000549111.5:n.97A>G

ENST00000551337.5:c.1A>G

ENST00000551988.5:n.90A>G

ENST00000553106.5:c.1A>G

ENST00000635500.1:n.29-4232A>G

Pathogenic

Met criteria codes **4**

PP4_Moderate **PS3** **PM3** **PM2**

Not Met criteria codes **1**

PVS1

Evidence Links **2**

Expert Panel

[Phenylketonuria VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM2: gnomAD MAF=0.00002; PP4_Moderate: Seen in PKU patients. BH4 disorders ruled out. (PMID:2574002); PS3: <3% (PMID:9450897). PM3: Detected in trans with known pathogenic variants. In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM2, PM3, PP4_Moderate, PS3). Updated to reflect new PVS1 recommendations.

Met criteria codes

PP4_Moderate	✓	Seen in PKU patients. BH4 disorders ruled out. <hr/> Analysis of RFLP haplotypes and mutations revealed a novel mutation, an A-to-G transition (met----val) in codon 1 (the translation-initiation codon). It occurred on 5 of the 18 mutant chromosomes. A proband homozygous for this mutation had the PKU phenotype. The appropriate biochemical tests were done to rule out disorders of tetrahydrobiopterin homeostasis. PubMed:2574002
PS3	✓	<3% <hr/> < 3 PAH enzyme activity as % of wild type. (p91023(B)/COS PubMed:9450897
PM3	✓	Detected in trans with c.1315+1G>A (known pathogenic), and also in the homozygous state. <hr/> A proband was homozygous for this mutation (A-to-G transition (met-val) in codon1]. In other probands, the codon1 mutation was inherited once with the splice junction mutation in exon 12 (c.1315+1G>A),and was inherited twice with a mutation on haplotype 1. PubMed:2574002
PM2	✓	gnomAD MAF=0.00002

Not Met criteria codes

PVS1	✗	Initiation codon variant
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Curation History [↗](#)

Showing 1 to 1 of 1 rows

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