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.1A>G (p.Met1Val)

Version: 1.0

CA114360

586 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 89f04437-ed5d-4735-8c4a-a9b1d91d10ea
Approved on: 2019-03-23
Published on: 2019-05-10

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

PS3 PM2 PM3 PP4_Moderate

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

PS3	✔	<3%
		< 3 PAH enzyme activity as % of wild type. (p91023(B)/COS PubMed:9450897
PM2	✔	gnomAD MAF=0.00002
PM3	✔	Detected in trans with c.1315+1G>A (known pathogenic), and also in the homozygous state.
		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
PP4_Moderate	✔	Seen in PKU patients. BH4 disorders ruled out.
		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

Not Met criteria codes

PVS1	✖	Initiation codon variant

Curation History

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