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.3G>A (p.Met1Ile)

Version: 1.0

CA229532

622 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6cb217d7-b360-4a26-8c17-bce833da85f1
Approved on: 2019/7/7
Published on: 2019/7/7

HGVS expressions

NM_000277.2(PAH):c.3G>A (p.Met1Ile)
NM_000277.2:c.3G>A
NC_000012.12:g.102917128C>T
CM000674.2:g.102917128C>T
NC_000012.11:g.103310906C>T
CM000674.1:g.103310906C>T
NC_000012.10:g.101835036C>T
NG_008690.1:g.5475G>A
NG_008690.2:g.46283G>A
ENST00000553106.6:c.3G>A
ENST00000307000.7:c.-145G>A
ENST00000546844.1:c.3G>A
ENST00000547319.1:n.314G>A
ENST00000549111.5:n.99G>A
ENST00000551337.5:c.3G>A
ENST00000551988.5:n.92G>A
ENST00000553106.5:c.3G>A
ENST00000635500.1:n.29-4230G>A
NM_000277.1:c.3G>A
NM_001354304.1:c.3G>A
NM_000277.3:c.3G>A
NM_001354304.2:c.3G>A

Pathogenic

Met criteria codes 6

PP1 PM2 PVS1 PS2_Moderate PM3_Strong PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.3G>A (p.Met1Ile) variant is a null variant (start loss) where LOF is a known mechanism of disease. There are no known alternative start codons in other transcripts. The next in-frame Met is at amino acid 180 in exon 6. There are 49 pathogenic variants in ClinVar upstream of aa 180. The p.Met1Val variant has <3% enzyme activity as compared to wild type (PMID: 9450897), confirming start loss variants lead to loss of function of the PAH enzyme without re-initiation. This variant has been detected in multiple patients with PKU, BH4 deficiency excluded. PMID: 1301947, 23514811 (PP4_Moderate). This variant is absent in population databases (PM2). This variant was detected in trans with pathogenic variants IVS12+1G>A (PMID: 1301947) and p.F55L (27121329) (PM3_Strong). This variant has been detected de novo (PS2_moderate; PMID: 1301947), and in affected siblings (PP1; 23514811) In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PVS1, PM2, PP4_Moderate, PS2_moderate, PP1.

Met criteria codes

PP1	✔	Cosegregation with disease in affected siblings (1 mPKU, 1 BHPA) . PMID: 23514811 Cosegregation with disease in affected siblings (1 mPKU, 1 BHPA) PubMed:23514811
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP
PVS1	✔	Null variant (start loss) where LOF is a known mechanism of disease. There are no known alternative start codons in other transcripts. The next in-frame Met is at amino acid 180 in exon 6. There are 49 pathogenic variants in ClinVar upstream of aa 180. The p.Met1Val variant has <3% enzyme activity as compared to wild type (PMID: 9450897), confirming start loss variants lead to loss of function of the PAH enzyme without re-initiation. Kept at full strength per Steven Harrison.
PS2_Moderate	✔	De novo (maternity and paternity confirmed in a patient with classical PKU. Strength decreased per SVI recommendations. He had inherited the IVS-12 mutation from his mother, and the haplotype 7 (hpt7) chromosome from his father. Since the paternal chromosome did not carry the M1I mutation, paternity testing was carried out. Fingerprint patterns were fully compatible with paternity. The M1I mutation was not found in his mother or in two healthy brothers. PubMed:1301947
PM3_Strong	✔	detected in trans with a pathogenic variants IVS12+1G>A (PMID: 1301947) and p.F55L (27121329) Same patients as Bueno, et al. Patients' and their families' genomic DNA was obtained from whole-blood samples and/or dried blood spots. Segregation analysis was done to rule out the presence of large genomic rearrangements. PubMed:27121329 The compound heterozygote genotype (IVS-12/M1I). He had inherited the IVS-12 mutation from his mother, and the haplotype 7 (hpt7) chromosome from his father. PubMed:1301947 Genotype in 2 siblings: p.M1I/F55L. PubMed:23514811
PP4_Moderate	✔	Detected multiple patients with PKU, BH4 deficiency excluded. PMID: 1301947, 23514811 We describe the detection of a de novo mutation in the phenylalanine hydroxylase gene in a Norwegian phenylketonuria (PKU) patient. This novel mutation, M1I, disrupts the start codon of the gene by a G to A transition. The compound heterozygote genotype (IVS-12/M1I) of this patient predicts that no phenylalanine hydroxylase

enzyme is formed, thus leading to a severe classical PKU. A pretreatment serum phenylalanine value of 1,592 umol/liter and a phenylalanine tolerance at age 4 years of 20 mg/kg/day in the patient. PubMed:1301947
Detected on 3 alleles. Patients with transient HPA or with HPA due to a defect in the synthesis or recycling of the cofactor BH4 were excluded. PubMed:23514811

Not Met criteria codes

PM5		✖	Loss of function start loss variant

Curation History

Showing 1 to 1 of 1 rows

See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000277.2(PAH):c.3G>A (p.Met1Ile)	Pathogenic	Phenylketonuria	2019-07-07	1.0	-	PAH

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
⌑ Powered by BCM's Genboree.