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_000277.1(PAH):c.916A>G (p.Ile306Val)

CA114365

618 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 168d68ba-4789-4c16-80f7-b3bd0197b5a8
Approved on: 2018-08-10
Published on: 2018-12-10

HGVS expressions

NM_000277.1:c.916A>G
NM_000277.1(PAH):c.916A>G (p.Ile306Val)
NC_000012.12:g.102846948T>C
CM000674.2:g.102846948T>C
NC_000012.11:g.103240726T>C
CM000674.1:g.103240726T>C
NC_000012.10:g.101764856T>C
NG_008690.1:g.75655A>G
NG_008690.2:g.116463A>G
NM_000277.2:c.916A>G
NM_001354304.1:c.916A>G
NM_000277.3:c.916A>G
ENST00000307000.7:c.901A>G
ENST00000549247.6:n.675A>G
ENST00000551114.2:n.578A>G
ENST00000553106.5:c.916A>G
ENST00000635477.1:n.74-2517A>G
ENST00000635528.1:n.431A>G

Pathogenic

Met criteria codes 5

PP3 PM3 PM2 PP4_Moderate PS3

Not Met criteria codes 1

PM5

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: MAF = 2.0e-5; PP3: Software agrees on a damaging effect.; PS3: Mutation ID#1, 18% residual enzyme activity (PMID:18590700); PM3: I306V / F55L (pathogenic in ClinVar) in a single patient with mild HPA (PMID:18299955);

PP4_Moderate: BH4 defect excluded in all patients--single patient with mild hyperphe (Bercovich, 2008). (PMID:18299955). 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, PP3, PS3, PM3, PP4_Moderate).

Met criteria codes

PP3	✔	Software agrees on a damaging effect.
PM3	✔	I306V / F55L (pathogenic in ClinVar) in a single patient with mild HPA Study in Israel. 200 PKU patients. Single patient with c.916A>G variant. PubMed:18299955
PM2	✔	MAF = 2.0e-5
PP4_Moderate	✔	BH4 defect excluded in all patients--single patient with mild hyperphe (Bercovich, 2008). General: Patients from Metabolic Disease Unit at Safra Childrens Hhospital, Sheba Medical Center. 400 patients, 200 different families—for this study 180 samples were collected. Looking at phenotype/genotype correlations in different ethnic groups in Israel. PubMed:18299955
PS3	✔	Mutation ID#1, 18% residual enzyme activity PAH activity analysis. Site directed mutagenesis, transfected COS-1 cells. Enzyme activity measured as conversion of L-[14C]phe to L-[14C]tyr. Use both standard cDNA expression system and a new Intinic plasmid system which incorporates intronic sequences. Standard cDNA method demonstrates 18% and intinic system demonstrates 15% residual enzyme activity PubMed:18590700

Not Met criteria codes

PM5	✖	No other variants identified in this codon

Curation History

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