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:c.1216A>G

CA6748709

619167 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 99c1aff1-c37d-4471-90f9-86d122e11e34
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HGVS expressions

NM_000277.1:c.1216A>G
NC_000012.12:g.102840499T>C
CM000674.2:g.102840499T>C
NC_000012.11:g.103234277T>C
CM000674.1:g.103234277T>C
NC_000012.10:g.101758407T>C
NG_008690.1:g.82104A>G
NG_008690.2:g.122912A>G
NM_000277.2:c.1216A>G
NM_001354304.1:c.1216A>G
NM_000277.3:c.1216A>G
ENST00000307000.7:c.1201A>G
ENST00000551114.2:n.878A>G
ENST00000553106.5:c.1216A>G
ENST00000635477.1:n.320A>G
ENST00000635528.1:n.731A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM5 PM2 PP4_Moderate

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1216A>G (p.Ile406Val) variant in PAH is reported in an individual with PKU. Dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading were collected. (PMID: 26503515) This variant has a low frequency in ExAC/gnomAD (MAF=0.00016) and is absent from 1000G. A deleterious effect is predicted by SIFT, Polyphen, and MutationTaster. Another missense variant at this amino acid is interpreted as likely pathogenic by our PAH VCEP (p.I406T). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM5, PP4_Moderate, PP3.

Met criteria codes

PP3	✔	Support a deleterious effect: deleterious by SIFt, possibly damaging by Polyphen, and damaging by MutationTaster
PM5	✔	I406T curated as likely pathogenic
PM2	✔	Low AF in ExAC/gnomAD: (MAF:0.00016) and absent from 1000G.
PP4_Moderate	✔	Seen in an individual with PKU. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PMID: 26503515. Seen in an individual with PKU. These patients were diagnosed at birth either through a neonatal screening program or based on clinical presentation. Biochemical testing data, including plasma phenylalanine (Phe) levels, dihydropteridine reductase activity, urinary biopterin and neopterin ratio, and tetrahydrobiopterin loading, were collected. PubMed:26503515

Curation History

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