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.1187A>G

Version: 1.0

CA6748729

962987 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 91666141-f09d-4a5e-ad19-0a1f56c377cb
Approved on: 2020/8/13
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HGVS expressions

NM_000277.1:c.1187A>G
NC_000012.12:g.102843658T>C
CM000674.2:g.102843658T>C
NC_000012.11:g.103237436T>C
CM000674.1:g.103237436T>C
NC_000012.10:g.101761566T>C
NG_008690.1:g.78945A>G
NG_008690.2:g.119753A>G
ENST00000553106.6:c.1187A>G
ENST00000307000.7:c.1172A>G
ENST00000549247.6:n.946A>G
ENST00000551114.2:n.849A>G
ENST00000553106.5:c.1187A>G
ENST00000635477.1:c.291A>G
ENST00000635528.1:n.702A>G
NM_000277.2:c.1187A>G
NM_001354304.1:c.1187A>G
NM_000277.3:c.1187A>G
NM_001354304.2:c.1187A>G

Likely Pathogenic

Met criteria codes 3

PM3 PM2 PP4_Moderate

Not Met criteria codes 1

PP3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1187A>G (p.Lys396Arg) variant in PAH has been reported in multiple individuals with mild HPA and PKU (BH4 deficiency excluded). (PMID: 21147011, 23357515). This variant has extremely low frequency in ExAC and gnomAD (MAF=0.00006). This variant was detected

with pathogenic variants IVS10-11G>A in 2 patients (PMID: 21147011) and p.Arg408Trp (PMID: 23357515). Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3.

Met criteria codes

PM3	✔	detected with IVS10-11G>A in 2 patients. parental analysis not reported PMID: 21147011; p.[Lys396Arg];[Arg408Trp] parental analysis not reported PMID: 23357515
PM2	✔	Absent from 1000G, ESP; extremely low frequency in ExAC (MAF=0.00006), gnomAD
PP4_Moderate	✔	K396R found in 1 mHPA (<600 µmol/L) patient and 1 mPKU patient (600–1200 µmol/L). BH4 deficiency excluded by assessment of PAH, PTS, and QDPR genes PMID: 21147011, PMID: 23357515

Not Met criteria codes

PP3	✖	Conflicting predictions of pathogenicity: Damaging in SIFT, MutationTaster, Benign/Neutral in Polyphen2

Curation History

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