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Variant: NM_000277.1:c.1218A>G

CA6748708

552907 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 855d18fc-6dd6-4938-9924-d6694afb9079
Approved on: 2018-12-09
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HGVS expressions

NM_000277.1:c.1218A>G
NC_000012.12:g.102840497T>C
CM000674.2:g.102840497T>C
NC_000012.11:g.103234275T>C
CM000674.1:g.103234275T>C
NC_000012.10:g.101758405T>C
NG_008690.1:g.82106A>G
NG_008690.2:g.122914A>G
NM_000277.2:c.1218A>G
NM_001354304.1:c.1218A>G
NM_000277.3:c.1218A>G
ENST00000307000.7:c.1203A>G
ENST00000551114.2:n.880A>G
ENST00000553106.5:c.1218A>G
ENST00000635477.1:n.322A>G
ENST00000635528.1:n.733A>G

Likely Pathogenic

Met criteria codes 4

PM5 PM3 PM2 PP4

Not Met criteria codes 1

PP3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1218A>G (p.Ile406Met) variant in PAH is reported in 2 individuals with non-PKU HPA. BH4 assessment was not stated. It was detected with a known pathogenic variant, p.Arg408Trp. (PMID: 23357515) This variant has a low allele frequency in gnomAD and ExAC (MAF=0.00003) and is absent in 1000G. Computational evidence is discordant. Another missense change at this amino acid is interpreted

as likely pathogenic by the 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, PM3, PM5, PP4.

Met criteria codes

PM5	✔	I406T curated as LP.
PM3	✔	genotype p.[Ile406Met];[Arg408Trp] PMID: 23357515 2 patients with the genotype p.[Ile406Met];[Arg408Trp] (VarID 577, Pathogenic). PubMed:23357515
PM2	✔	Low AF (gnomAD,ExAC MAF=0.00003) and absent in 1000G
PP4	✔	Seen in an individual with non HPA PKU or mild PKU. PMID: 23357515 Seen in an individual with non HPA PKU or mild PKU. Predicted to have a 'less deleterious' effect. PubMed:23357515

Not Met criteria codes

PP3	✖	Discordant results- tolerated by SIFT and damaging by PolyPhen and MutTaster

Curation History

Showing 1 to 1 of 1 rows

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