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Variant: NM_000277.1:c.668A>T

Version: 1.0

CA6748885

549912 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5a15de96-3e5f-4ae6-8e63-788d59a55987
Approved on: 2020/6/1
Published on: 2021/10/10

HGVS expressions

NM_000277.1:c.668A>T
NC_000012.12:g.102855174T>A
CM000674.2:g.102855174T>A
NC_000012.11:g.103248952T>A
CM000674.1:g.103248952T>A
NC_000012.10:g.101773082T>A
NG_008690.1:g.67429A>T
NG_008690.2:g.108237A>T
ENST00000553106.6:c.668A>T
ENST00000307000.7:c.653A>T
ENST00000549111.5:n.764A>T
ENST00000553106.5:c.668A>T
NM_000277.2:c.668A>T
NM_001354304.1:c.668A>T
NM_000277.3:c.668A>T
NM_001354304.2:c.668A>T

Likely Pathogenic

Met criteria codes 4

PP3 PM3 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.668A>T (p.Asn223Ile) variant in PAH has been reported in 2 individuals with PKU and MHP (BH4 deficiency excluded). (PMID: 30050108). This variant has extremely low frequency in gnomAD (MAF=0.0001307). This variant was detected with in trans with p.Y166* (PMID: 30050108). Computational evidence supports a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP3	✔	predicted deleterious in SIFT, Polyphen2, MutationTaster
PM3	✔	detected in trans with p.Y166* (P 2 submitters) The validation tests on parents were performed. PMID: 30050108
PM2	✔	Extremely low frequency in ExAC and gnomAD (MAF=0.0001307)
PP4_Moderate	✔	N223I found on 2 alleles of PKU patients. BH4 cofactor deficiency assessed. Upgraded per ClinGen PAHEP. PMID: 30050108

796 PKU patients from mainland China diagnosed at birth either through a neonatal screening program or based on clinical presentation. N223I found on 2 alleles. PubMed:26503515

Curation History

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