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Variant: NM_000277.1(PAH):c.673C>G (p.Pro225Ala)

Version: 1.0

CA229686

102780 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: a087e449-d830-49e4-bceb-5990ab49123a
Approved on: 2021/2/14
Published on: 2021/6/9

HGVS expressions

NM_000277.1(PAH):c.673C>G (p.Pro225Ala)
NM_000277.1:c.673C>G
NC_000012.12:g.102855169G>C
CM000674.2:g.102855169G>C
NC_000012.11:g.103248947G>C
CM000674.1:g.103248947G>C
NC_000012.10:g.101773077G>C
NG_008690.1:g.67434C>G
NG_008690.2:g.108242C>G
ENST00000553106.6:c.673C>G
ENST00000307000.7:c.658C>G
ENST00000549111.5:n.769C>G
ENST00000553106.5:c.673C>G
NM_000277.2:c.673C>G
NM_001354304.1:c.673C>G
NM_000277.3:c.673C>G
NM_001354304.2:c.673C>G

Likely Pathogenic

Met criteria codes 4

PP3 PM5 PM2 PP4_Moderate

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.673C>G (p.Pro225Ala) variant in PAH has been reported in 1 individual with classic PKU (BH4 deficiency excluded, PMID: 29499199). This variant is absent in population databases. Multiple lines of computational evidence support a deleterious effect. Another missense change at the same amino acid, p.Pro225Thr, is interpreted as pathogenic by multiple submitters in ClinVar (variation ID 102779). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM5, PP3.

Met criteria codes

PP3	✔	Predicted deleterious in SIFT, PolyPhen2, MutationTaster, REVEL=0.986
PM5	✔	p.P225T pathogenic 2 submitters
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, ESP
PP4_Moderate	✔	Detected in a Chinese patient with classic PKU. urinary pterin analysis and a DHPR activity assay were also carried out to distinguish between PAH deficiency and tetrahydrobiopterin deficiency, in addition to sequencing of PAH, PTS, QDPR, GCH1 and PCBD1genes. PMID: 29499199

Curation History

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