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Variant: NM_000277.2(PAH):c.523C>T (p.Pro175Ser)

Version: 1.0

CA16020810

555366 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 668b6965-0eb2-46ca-a2a6-80d7f55a3bf1
Approved on: 2019-04-08
Published on: 2019-04-08

HGVS expressions

NM_000277.2:c.523C>T
NM_000277.2(PAH):c.523C>T (p.Pro175Ser)
NC_000012.12:g.102855319G>A
CM000674.2:g.102855319G>A
NC_000012.11:g.103249097G>A
CM000674.1:g.103249097G>A
NC_000012.10:g.101773227G>A
NG_008690.1:g.67284C>T
NG_008690.2:g.108092C>T
NM_000277.1:c.523C>T
NM_001354304.1:c.523C>T
NM_000277.3:c.523C>T
ENST00000307000.7:c.508C>T
ENST00000549111.5:n.619C>T
ENST00000551988.5:n.544C>T
ENST00000553106.5:c.523C>T

Likely Pathogenic

Met criteria codes 4

PM2 PM3 PP4_Moderate 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.523C>T (p.Pro175Ser) variant in PAH has been reported in 1 individual with classic PKU (BH4 deficiency excluded) in trans with pathogenic variant p.R413P (PP4_Moderate, PM3; PMID: 26322415). This variant is absent in population databases (PM2). Computational evidence support a deleterious effect (PP3). 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

PM2	✔	Absent from controls in ExAC/gnomAD, 1000 Genomes, ESP
PM3	✔	detected in trans with p.R413P (P, 6 submitters) PMID: 26322415 Patient genotype: c.[523C>T];[1238G>C], p.[P175S];[R413P]. All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing. PubMed:26322415
PP4_Moderate	✔	P175S detected in a patient with classic PKU. BH4 deficiency was excluded. PMID: 26322415 P175S detected in a patient with classic PKU. All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2 mg/dl. BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415
PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, Polyphen2, MutationTaster, REVEL=0.851)

Curation History

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