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Variant: NM_000277.2(PAH):c.591G>C (p.Leu197Phe)

Version: 1.0

CA267662

120280 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0de1731a-9fea-445e-ac38-11ce147f981a
Approved on: 2019-05-04
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HGVS expressions

NM_000277.2:c.591G>C
NM_000277.2(PAH):c.591G>C (p.Leu197Phe)
NC_000012.12:g.102855251C>G
CM000674.2:g.102855251C>G
NC_000012.11:g.103249029C>G
CM000674.1:g.103249029C>G
NC_000012.10:g.101773159C>G
NG_008690.1:g.67352G>C
NG_008690.2:g.108160G>C
NM_000277.1:c.591G>C
NM_001354304.1:c.591G>C
NM_000277.3:c.591G>C
ENST00000307000.7:c.576G>C
ENST00000549111.5:n.687G>C
ENST00000553106.5:c.591G>C

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.591G>C (p.Leu197Phe) variant in PAH has been reported in 3 individuals with classic PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 18299955). This variant is absent in population databases (PM2). This variant was detected with a pathogenic variant (c.168+1G>A) and twice in the homozygous state (PM3). Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.82). 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	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.82)
PM3	✔	Detected with IVS2+1G>A (c.168+1G>A), and homozygous in 2 patients. IVS2+1G>A (P by PAH WG) in 1 patient, homozygous in 2 patients. To identify homozygous mutations, 10 ll PCR product of wild-type DNA and 10 ll PCR product of sample DNA were mixed 1.1 and denatured at 95°C. This enabled detection of homozygous mutations by formation of a heteroduplex. PubMed:18299955
PM2	✔	Absent from ExAC, gnomAD, 1000 Genomes, ESP
PP4_Moderate	✔	L197F was detected in a patient with classic PKU (>20 mg/dl). BH4 deficiency was excluded. PMID: 18299955 All samples reported in this paper are PKU patients detected after neonatal screening. The patients were tested for the exclusion of lacking the cofactor BH4. L197F was detected in a patient with classic PKU (>20 mg/dl). PubMed:18299955

Curation History

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