The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.1:c.773T>C

CA16020855

619159 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 5bb26a8d-7e21-4fb6-93c4-a25021d88ba1
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HGVS expressions

NM_000277.1:c.773T>C
NC_000012.12:g.102852884A>G
CM000674.2:g.102852884A>G
NC_000012.11:g.103246662A>G
CM000674.1:g.103246662A>G
NC_000012.10:g.101770792A>G
NG_008690.1:g.69719T>C
NG_008690.2:g.110527T>C
NM_000277.2:c.773T>C
NM_001354304.1:c.773T>C
NM_000277.3:c.773T>C
ENST00000307000.7:c.758T>C
ENST00000549247.6:n.532T>C
ENST00000553106.5:c.773T>C

Likely Pathogenic

Met criteria codes 4

PP3 PM2 PP4_Moderate PM3_Supporting

Not Met criteria codes 1

PM5

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.773T>C (p.Leu258Pro) variant in PAH has been reported in 3 individuals with mild PKU (BH4 deficiency excluded). (PP4_Moderate; PMID: 19786003, 23514811). This variant is absent in population databases (PM2). This variant was present in two homozygous patients. Genetic analysis in parents confirmed homozygosity. PMID: 23514811 (PM3-supporting). 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_supporting, PP3.

Met criteria codes

PP3	✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.972
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP
PP4_Moderate	✔	L258P seen in 1 patient with mild PKU. Other causes of hyperphenylananinemia had been ruled out. PMID: 19786003 Twenty-five PKU patients, from 20 unrelated families, collected over 4-year period (2003–2006) were included in the study. Patients were diagnosed after presenting clinical symptoms using plasma and urinary amino acids analysis by TLC. Positive cases were confirmed by fluorometric assay determining serum phenylalanine levels. Patients were classified as having PKU when their serum phenylalanine levels exceeded 600 µmol/L before treatment and when other causes of hyperphenylalaninemia had been ruled out. In one patient we have identified a novel mutation p.L258P (c.773T>C) in homozygous fashion associated with the milder form of the disease. PubMed:19786003
PM3_Supporting	✔	p.L258P is present in two mild PKU homozygous patients. Genetic analysis in parents confirmed that the patients are homozygous. PMID: 23514811 Table 3. Patient 14. p.L258P on both alleles. p.L258P is present in two mild PKU homozygous patients. Genetic analysis in parents confirmed that the patients are homozygous. PubMed:23514811

Not Met criteria codes

PM5	✖	No ClinVar variants in this codon

Curation History

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