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_000277.2(PAH):c.746T>A (p.Leu249His)

Version: 1.0

CA229740

102822 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 81d113f5-3c37-433a-9d29-c6e268cb045f
Approved on: 2020/11/13
Published on: 2022/3/11

HGVS expressions

NM_000277.2(PAH):c.746T>A (p.Leu249His)
NM_000277.2:c.746T>A
NC_000012.12:g.102852911A>T
CM000674.2:g.102852911A>T
NC_000012.11:g.103246689A>T
CM000674.1:g.103246689A>T
NC_000012.10:g.101770819A>T
NG_008690.1:g.69692T>A
NG_008690.2:g.110500T>A
ENST00000553106.6:c.746T>A
ENST00000307000.7:c.731T>A
ENST00000549247.6:n.505T>A
ENST00000553106.5:c.746T>A
NM_000277.1:c.746T>A
NM_001354304.1:c.746T>A
NM_000277.3:c.746T>A
NM_001354304.2:c.746T>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PM5 PM2 PP3 PP4

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.746T>A (p.Leu249His) variant in PAH has been reported in 1 individual with mild PKU (PMID: 11360625). This variant is absent in population databases. This variant was detected with pathogenic variant p.R243Q (PMID: 16256386). Computational evidence supports a deleterious effect. Another missense change at the same amino acid (p.L249F) is interpreted as pathogenic by multiple submitters. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM5, PM3_supporting, PP3, PP4.

Met criteria codes

PM3_Supporting	✔	L249H detected with R243Q, Pathogenic. Maternal or paternal inheritance of mutations was determined when parental DNA was available PMID: 16256386 Patient Genotype R243Q (VarID 591, Pathogenic) + L249H PubMed:16256386
PM5	✔	L249F is Pathogenic
PM2	✔	Absent from ExAC, 1000G, ESP, gnomAD
PP3	✔	Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.977
PP4	✔	L249H found in 1 patient with mild PKU. BH4 deficiency not ruled out. PMID: 11360625, PMID: 16256386 185 patients with PAH deficiency in 185 independent families from Northern China are included in this study. PAH deficiency was diagnosed by conventional biochemical methods. L249H (c.746T>A) was found on 1 allele in a patient with mild PKU (Phe 600–1200 umol/L). PubMed:16256386 Exon 7 of the PAH gene was analyzed in 45 children affected with classic PKU from northern China. L249H was identified. PubMed:11360625

Curation History

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