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_000277.3(PAH):c.1162G>C (p.Val388Leu)

Version: 1.0

CA229366

102541 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 77049e4f-86fd-47f5-9095-13c4877981c6
Approved on: 2020/10/16
Published on: 2020/10/16

HGVS expressions

NM_000277.3(PAH):c.1162G>C (p.Val388Leu)
NM_000277.3:c.1162G>C
NC_000012.12:g.102843683C>G
CM000674.2:g.102843683C>G
NC_000012.11:g.103237461C>G
CM000674.1:g.103237461C>G
NC_000012.10:g.101761591C>G
NG_008690.1:g.78920G>C
NG_008690.2:g.119728G>C
ENST00000553106.6:c.1162G>C
ENST00000307000.7:c.1147G>C
ENST00000549247.6:n.921G>C
ENST00000551114.2:n.824G>C
ENST00000553106.5:c.1162G>C
ENST00000635477.1:c.266G>C
ENST00000635528.1:n.677G>C
NM_000277.1:c.1162G>C
NM_000277.2:c.1162G>C
NM_001354304.1:c.1162G>C
NM_001354304.2:c.1162G>C

Pathogenic

Met criteria codes 4

PM5 PM2 PP4_Moderate PM3_Strong

Not Met criteria codes 1

PP3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This c.1162G>C (p.Val388Leu) variant in PAH was reported in 3 patients with PAH deficiency (PMID: 27121329, 31623983) detected with the likely pathogenic variant p.Pro281Leu and the pathogenic variant p.Arg252Trp. DHPR activity, biopterin and/or pteridine analysis was performed to rule out other causes of hyperphenylalaninemia (PMID: 27121329). This variant is a novel missense change at an amino acid residue where a different missense change p.Val388Met determined to be pathogenic has been seen before. This variant is present in Dominican populations at a minor allele frequency of 0.00052 (PAGE study). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP4_moderate.

Met criteria codes

PM5	✔	PM5_met: 2 other missense variants at this residue in ClinVar: p.Val388Met P by 5 submitters and PAH EP (expert panel); p.Val388Ala LP by PAH EP
PM2	✔	PM2_met: This variant is absent from population databases gnomAD and ExAC. This variant is present in Dominican populations at a minor allele frequency of 0.00052 (3828 chromosomes)(PAGE study).
PP4_Moderate	✔	PP4_moderate: This variant was documented 1 time in a patient with PAH deficiency. A defect in the synthesis or regeneration pathways of 6R-BH4 was ruled out by analyzing urinary pterin levels as well as by measuring the dihydropteridine reductase activity (PMID: 27121329) 27121329, Aldámiz-Echevarría: This variant was documented 1 time in a Spanish patient with moderate PKU (MPKU). Phenylalanine plasma concentrations >120 µM were reported for all subjects. Tetrahydrobiopterin (BH4) deficiency was excluded through a BH4 loading test, urinary pterin analysis and DHPR activity assay.
PM3_Strong	✔	PM3_strong: This variant was detected in trans with a likely pathogenic variant in 1 patient with moderate PKU (PMID: 27121329). This variant was detected in trans with a pathogenic variant in 2 patients with mild hyperphenylalaninemia (MHP)(PMID: 31623983). 27121329 - This variant was detected in trans with the likely pathogenic PAH variant p.Pro281Leu in 1 patient with moderate PKU. Parental analysis was performed to confirm compound heterozygosity. 31623983 - This variant was detected in trans with the pathogenic PAH variant p.Arg252Trp in 2 patients with mild hyperphenylalaninemia (MHP). Parental analysis was not performed to confirm compound heterozygosity.

PubMed:31623983
PubMed:27121329
PubMed:9452061

Not Met criteria codes

PP3	✖	PP3_not met: Predicted to be tolerated (SIFT), benign (PolyPhen2), disease causing (MutationTaster). REVEL=0.678

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.