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Variant: NM_000277.3(PAH):c.1229T>C (p.Phe410Ser)

Version: 1.0

CA229405

102571 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 01797166-5f8d-47c6-91c4-0a5273521d2c
Approved on: 2025/8/15
Published on: 2025/8/15

HGVS expressions

NM_000277.3:c.1229T>C
NM_000277.3(PAH):c.1229T>C (p.Phe410Ser)
NC_000012.12:g.102840486A>G
CM000674.2:g.102840486A>G
NC_000012.11:g.103234264A>G
CM000674.1:g.103234264A>G
NC_000012.10:g.101758394A>G
NG_008690.1:g.82117T>C
NG_008690.2:g.122925T>C
ENST00000553106.6:c.1229T>C
ENST00000307000.7:c.1214T>C
ENST00000551114.2:n.891T>C
ENST00000553106.5:c.1229T>C
ENST00000635477.1:c.333T>C
ENST00000635528.1:n.744T>C
NM_000277.1:c.1229T>C
NM_000277.2:c.1229T>C
NM_001354304.1:c.1229T>C
NM_001354304.2:c.1229T>C

Pathogenic

Met criteria codes 5

PP3_Strong PM3 PM5 PP4_Moderate PM2_Supporting

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.3(PAH):c.1229T>C variant in PAH is a missense variant predicted to cause substitution of phenylalanine to serine at amino acid 410 (p.Phe410Ser). At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) and sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism which is highly specific for Phenylketonuria (PP4_moderate; PMIDs:26542770, 10679941). This variant has been detected in 2 individuals with Phenylketonuria. Of those individuals, both were compound heterozygous for the variant and distinct likely pathogenic p.P281L (parental testing was not reported) and pathogenic p.I306V (in trans) variants (PM3; PMID: 26542770). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000008476 in European (non-Finnnish) population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.992, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong). Two different missense variants, c.1229T>G (p.Phe410Cys) and c.1229T>G (p.Phe410Cys) are in the same codon have been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2_supporting, PM3, PP3_strong, PP4_moderate, PM5. Version 2.0, 7/16/2024.

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.992, which meets the threshold of 0.932, evidence that correlates with strong impact to PAH function (PP3_Strong).
PM3	✔	This variant has been detected in 2 individuals with Phenylketonuria. Of those individuals, both were compound heterozygous for the variant and distinct likely pathogenic p.P281L (parental testing was not reported) and pathogenic p.I306V (in trans) variants (PMID: 26542770).
PM5	✔	Two different missense variants, c.1229T>G (p.Phe410Cys) and c.1229T>G (p.Phe410Cys) are in the same codon have been classified as likely pathogenic for PAH deficiency by the ClinGen PAH Variant Curation Expert Panel (PM5).
PP4_Moderate	✔	At least one patient with this variant displayed plasma phenylalanine concentration persistently above 120umol/L (2mg/dL) and sequencing of genes in the BH4 cofactor metabolism pathway to exclude a defect of BH4 cofactor metabolism which is highly specific for Phenylketonuria (PMIDs:26542770, 10679941).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000008476 in European (non-Finnnish) population, which is lower than the ClinGen PAH Variant Curation Expert Panel threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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