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:c.521T>A

Version: 1.0

CA6748896

2137408 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 932ef138-55a5-46b1-bd7e-4dee89157e89
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HGVS expressions

NM_000277.3:c.521T>A
NC_000012.12:g.102855321A>T
CM000674.2:g.102855321A>T
NC_000012.11:g.103249099A>T
CM000674.1:g.103249099A>T
NC_000012.10:g.101773229A>T
NG_008690.1:g.67282T>A
NG_008690.2:g.108090T>A
ENST00000553106.6:c.521T>A
ENST00000307000.7:c.506T>A
ENST00000549111.5:n.617T>A
ENST00000551988.5:n.542T>A
ENST00000553106.5:c.521T>A
NM_000277.1:c.521T>A
NM_000277.2:c.521T>A
NM_001354304.1:c.521T>A
NM_001354304.2:c.521T>A

Likely Pathogenic

Met criteria codes 5

PP3_Moderate 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 c.521T>A variant in PAH is a missense variant predicted to cause substitution of Isoleucine by Asparagine at amino acid 174 (p.Ile174Asn). At least one patient with this variant displayed plasma phenylalanine > 1.2 mmol/L, which is highly specific for PAH deficiency; BH4 deficiency was excluded by analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine (PP4_Moderate; PMID: 21307867, 23842451). Additional individuals with PAH deficiency were compound heterozygous for the variant and a pathogenic variant (phase unknown; c.1315+1G>A, p.P211T, 1.0 point, PMID: 23842451. The highest population minor allele frequency in gnomAD v4.1 is 0.00008010, which is lower than the ClinGen PAH threshold (<0.0002) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a SCORE of 0.929, which is between the threshold of 0.773 - 0.932, evidence that correlates with moderate impact to PAH function (PP3_moderate). In summary, this variant meets criteria to be classified as likely pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH VCEP: PP4_Moderate, PM2_supporting, PM3, PP3_moderate.

Met criteria codes

PP3_Moderate	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, PolyPhen2, MutationTaster, REVEL=0.929)
PM3	✔	Detected with 2 pathogenic variants, phase unknown: c.1315+1G>A (P, 13 submitters); p.P211T (P by VCEP) PMID: 23842451. PMID: 27173423 is phase unknown, no points apply. P299C not in ClinVar. PMID: 32668217 is phase unknown, unsure if unrelated probands, not applying points for multiple individuals.
PM5	✔	I174T/V are P/LP by PAH VCEP
PP4_Moderate	✔	I174N was detected in 2 Japanese patients (classical PKU, plasma phe > 1.2 mmol/L; Mild HPA, plasma phe 0.18-0.6 mmol/L. BH4 deficiency excluded by Analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine. PMID: 21307867
PM2_Supporting	✔	extremely low frequency in gnomAD v4.1 (MAF=0.00002228 East Asian)

Curation History

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