

Variant: *NM_001354304.2:c.1071C>A*

Version: 1.0

CA16020933 [↗](#)

1065374 (ClinVar) [↗](#)

Gene: PAH ([HGNC:5053](#))

Condition: phenylketonuria ([MONDO:0009861](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: a93e52bd-88fe-43c5-b618-e25cef43653f

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HGVS expressions

NM_001354304.2:c.1071C>A
NC_000012.12:g.102843774G>T
CM000674.2:g.102843774G>T
NC_000012.11:g.103237552G>T
CM000674.1:g.103237552G>T
NC_000012.10:g.101761682G>T
NG_008690.1:g.78829C>A
NG_008690.2:g.119637C>A
ENST00000553106.6:c.1071C>A
ENST00000307000.7:c.1056C>A
ENST00000549247.6:n.830C>A
ENST00000551114.2:n.733C>A
ENST00000553106.5:c.1071C>A
ENST00000635477.1:c.175C>A
ENST00000635528.1:n.586C>A
NM_000277.1:c.1071C>A
NM_000277.2:c.1071C>A
NM_001354304.1:c.1071C>A
NM_000277.3:c.1071C>A

Pathogenic

Met criteria codes **4**

PVS1 PP4_Moderate PM2
PM3_Strong

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

This variant c.1071C>A (p.Cys357Ter) in PAH was reported with pathogenic variants p.Val399=, p.Arg243Gln and c.721C>T in 3 patients with PAH deficiency. BH4 deficiency was excluded through a BH4 loading test, urinary pterin analysis, and DHPR activity assay for 1 patient. (PMID: 28754886, 28982351, 31445982). This is a nonsense variant in exon 11 out of 13 coding exons, predicted to undergo

nonsense mediated mRNA decay. The exon is present in biologically-relevant transcripts. This variant is absent in population databases. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM3 strong, PM2, PP4 moderate.

Met criteria codes

PVS1			This is a nonsense variant in exon 11 out of 13 coding exons. The variant is predicted to undergo nonsense mediated decay (NMD), as it is not located in the 3'-most exon or the 3'-most 50 bp of the penultimate exon. The exon is present in biologically-relevant transcripts. Loss of function is a known mechanism of disease: 175 pathogenic null variants were reported in ClinVar for this gene across 13 different exons, 24 of which are in exon 11.
PP4_Moderate			This variant was documented in 2 patients with classic PKU (>1,200 µmol/L Phe) and 1 patient with mild PKU (360-600 µmol/L). For the mild PKU patient BH4 deficiency was excluded through a BH4 loading test, urinary pterin analysis, and DHPR activity assay. (PMID: 28754886, 28982351, 31445982)
PM2			This variant is absent from population databases gnomAD, 1000 Genomes and ESP.
PM3_Strong			This variant was detected in 2 patients with a PKU phenotype, it was not specified whether the patients genotypes were homozygous or compound heterozygous for the variant. p.Arg243Gln(P) .5pts, c.721C>T(P) .5pts, and detected in trans in 1 patient with a classic PKU phenotype p.Val399= (P) 1.0pts (PMID: 28754886, 28982351, 31445982)

Curation History

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