

Variant: *NM_001354304.2:c.1318G>T*

Version: 1.0

CA16020997 [↗](#)

932274 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 69793eba-f1b8-4e7f-af42-b3a459a72236

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HGVS expressions

NM_001354304.2:c.1318G>T
NC_000012.12:g.102839216C>A
CM000674.2:g.102839216C>A
NC_000012.11:g.103232994C>A
CM000674.1:g.103232994C>A
NC_000012.10:g.101757124C>A
NG_008690.1:g.83387G>T
NG_008690.2:g.124195G>T
ENST00000553106.6:c.1318G>T
ENST00000307000.7:c.1303G>T
ENST00000551114.2:n.980G>T
ENST00000553106.5:c.1318G>T
ENST00000635477.1:c.422G>T
ENST00000635528.1:n.833G>T
NM_000277.1:c.1318G>T
NM_000277.2:c.1318G>T
NM_001354304.1:c.1318G>T
NM_000277.3:c.1318G>T

Likely Pathogenic

Met criteria codes **4**

PM3_Supporting **PP4** **PM2**
PVS1_Strong

Evidence Links **0**

Expert Panel

[Phenylketonuria VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1318G>T (p.E440*) is a nonsense variant in exon 13 of 13 of PAH, a gene where loss of function is a known disease mechanism, and is predicted to lead to premature truncation of the protein at amino acid 440/453 (**PVS1_Strong**). Exon 13 encodes 15 amino acids + stop codon = 3.3% of PAH protein length. Along with Exon 12, Exon 13 forms the oligomerization domain (residues 411-452), which is responsible for the dimerization and tetramerization of the enzyme, important for regulation of PAH activity (e.g., positive cooperativity by

the substrate, L-Phe, and decreasing PAH activity at low L-Phe concentration) (see PMID: 23457044; PMID: 22005392). Exon 13 contains the non-truncating Likely Pathogenic p.A447P (Likely Pathogenic by ClinGen PAH VCEP) and Pathogenic p.A447D variants (Likely Pathogenic by ClinGen PAH VCEP; Pathogenic in Clinvar (ID 102595; 4 submitters, 2 stars). Thus PVS1_Strong will be applied for variants resulting in premature truncation of this exon. The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2). It has been previously reported in one proband with abnormal blood Phe (BH4 deficiency does not appear to have been formally excluded) (PP4) (PMID: 23842451), in presumed trans with the p.R243* mutation (Pathogenic per PAH VCEP) (0.5 points; PM3_Supporting). Classification: Likely Pathogenic Supporting Criteria: PVS1_Strong; PM2; PM3_Supporting; PP4

Met criteria codes

PM3_Supporting			(PMID: 23842451) in presumed trans with the p.R243* mutation (Pathogenic per PAH VCEP) (0.5 points; PM3_Supporting).
PP4			It has been previously reported in one proband with abnormal blood Phe (BH4 deficiency does not appear to have been formally excluded) (PP4) (PMID: 23842451), in presumed trans with the p.R243* mutation (Pathogenic per PAH VCEP) (0.5 points; PM3_Supporting).
PM2			The variant is absent from ethnically diverse control databases, including gnomAD/ExAC, 1000 Genomes, and ESP (PM2).
PVS1_Strong			The c.1318G>T (p.E440*) is a nonsense variant in exon 13 of 13 of PAH, a gene where loss of function is a known disease mechanism, and is predicted to lead to premature truncation of the protein at amino acid 440/453 (PVS1_Strong). Exon 13 encodes 15 amino acids + stop codon = 3.3% of PAH protein length. Along with Exon 12, Exon 13 forms the oligomerization domain (residues 411–452), which is responsible for the dimerization and tetramerization of the enzyme, important for regulation of PAH activity (e.g., positive cooperativity by the substrate, L-Phe, and decreasing PAH activity at low L-Phe concentration) (see PMID: 23457044; PMID: 22005392). Exon 13 contains the non-truncating Likely Pathogenic p.A447P (Likely Pathogenic by ClinGen PAH VCEP) and Pathogenic p.A447D variants (Likely Pathogenic by ClinGen PAH VCEP; Pathogenic in Clinvar (ID 102595; 4 submitters, 2 stars). Thus PVS1_Strong will be applied for variants resulting in premature truncation of this exon

Curation History

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