

Variant: NM_001354304.2:c.548A>G

Version: 1.0

CA16020814 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 89040e57-f09d-4602-82a0-0051fcd93944

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HGVS expressions

NM_001354304.2:c.548A>G

NC_000012.12:g.102855294T>C

CM000674.2:g.102855294T>C

NC_000012.11:g.103249072T>C

CM000674.1:g.103249072T>C

NC_000012.10:g.101773202T>C

NG_008690.1:g.67309A>G

NG_008690.2:g.108117A>G

ENST00000553106.6:c.548A>G

ENST00000307000.7:c.533A>G

ENST00000549111.5:n.644A>G

ENST00000551988.5:n.569A>G

ENST00000553106.5:c.548A>G

NM_000277.1:c.548A>G

NM_000277.2:c.548A>G

NM_001354304.1:c.548A>G

NM_000277.3:c.548A>G

Pathogenic

Met criteria codes 5

PP4_Moderate

PS3_Supporting

PM3_Strong

PP3_Strong

PM2_Supporting

Not Met criteria codes 1

PM5

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

This c.548A>G (p.Glu183Gly) variant in PAH was reported in trans with pathogenic variants p.Arg111* and c.721C>T in 2 patients with PAH deficiency (>120 μmol/L Phe, BH4 deficiency excluded) (PMID: 28982351, 28754886). Residual enzyme activity was 9.1% for p.Glu183Gly compared to the wild-type PAH (PMID: 24327145). Computational evidence for this missense variant is predicted to be damaging (REVEL=0.977). This variant is absent from population databases gnomAD. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2_supporting, PP4_moderate, PP3_strong, PS3_supporting.

Met criteria codes

PP4_Moderate			Detected in 2 patients with PAH deficiency (>120umol/L Phe). BH4 deficiency was excluded through a BH4 loading test, urinary pterin analysis, and DHPR activity assay for 1 patient. PMID: 28982351, 28754886
PS3_Supporting			Expression vectors containing PAH cDNA were constructed, residual enzyme activity was measured and found to be 9.1% for p.Glu183Gly compared to the wild-type PAH. Information from the abstract. PMID: 24327145
PM3_Strong			This variant was detected 2 times in trans with pathogenic PAH variants p.Arg111* (1.0pts) and c.721C>T (1.0pts) PMID: 28982351, 28754886
PP3_Strong			Computational evidence for this missense variant is predicted to be damaging (SIFT), probably damaging (PolyPhen2), and disease causing (MutationTaster). REVEL=0.977.
PM2_Supporting			This variant is absent from population databases gnomAD, 1000 Genomes, and ESP

Not Met criteria codes

PM5			p.Glu183Leu is classified as likely pathogenic
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Curation History



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