

Variant: *NM_000277.1(PAH):c.1039C>T (p.Leu347Phe)*

Version: 2.0

CA229296 [↗](#)

102488 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ff17bdce-39eb-49fe-bc18-7aab80634091

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HGVS expressions

NM_000277.1(PAH):c.1039C>T (p.Leu347Phe)

NM_000277.1:c.1039C>T

NC_000012.12:g.102844362G>A

CM000674.2:g.102844362G>A

NC_000012.11:g.103238140G>A

CM000674.1:g.103238140G>A

NC_000012.10:g.101762270G>A

NG_008690.1:g.78241C>T

NG_008690.2:g.119049C>T

ENST00000553106.6:c.1039C>T

ENST00000307000.7:c.1024C>T

ENST00000549247.6:n.798C>T

ENST00000551114.2:n.701C>T

ENST00000553106.5:c.1039C>T

ENST00000635477.1:c.143C>T

ENST00000635528.1:n.554C>T

NM_000277.2:c.1039C>T

NM_001354304.1:c.1039C>T

NM_000277.3:c.1039C>T

NM_001354304.2:c.1039C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PP3_Strong

PP4_Moderate

PM3_Supporting

Not Met criteria codes 2

BP4

PM5

Evidence Links 2

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**

Phenylketonuria VCEP

The c.1039C>T (p.Leu347Phe) variant in PAH has been reported twice in patients with PAH deficiency with BH4 deficiency excluded (PMID: 8659548, 21147011) (PP4_Moderate). One of these individuals was homozygous for the variant (PMID: 21147011) (PM3_Supporting). This variant is absent in population databases (PM2_Supporting). Multiple lines of computational evidence support a deleterious effect, including REVEL score 0.951 (PP3_Strong). In summary, this variant meets criteria to be classified as likely pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: PM2_Supporting, PP4_Moderate, PM3_Supporting, PP3_Strong.

Met criteria codes

PM2_Supporting			Absent from gnomAD v4.1.0
PP3_Strong			Predicted deleterious in SIFT, Polyphen2, MutationTaster, REVEL=0.951
PP4_Moderate			L347F found in 2 hyperphenylalaninemic patients. BH4 deficiency excluded in 1 patient Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 8659548, PMID: 21147011 588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). L347F found in homozygous state in 1 patient. PubMed:21147011 149 hyperphenylalaninemic females. L347F seen on 1 allele. PubMed:8659548
PM3_Supporting			PMID: 21147011: L347F found in homozygous state in 1 patient. parental analysis not reported (0.5pts) L347F found in homozygous state in 1 patient. PubMed:21147011

Not Met criteria codes

BP4			Predicted deleterious in SIFT, Polyphen2, MutationTaster
PM5			Only variant in codon

Curation History

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