

Variant: *NM_000277.1:c.877T>A*

Version: 1.0

CA16020883 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 8bbf7e43-d36e-4e46-a5b9-d90f4c029bb7

Approved on: 2024/9/6

Published on: 2025/8/2

HGVS expressions

NM_000277.1:c.877T>A

NC_000012.12:g.102851722A>T

CM000674.2:g.102851722A>T

NC_000012.11:g.103245500A>T

CM000674.1:g.103245500A>T

NC_000012.10:g.101769630A>T

NG_008690.1:g.70881T>A

NG_008690.2:g.111689T>A

ENST00000553106.6:c.877T>A

ENST00000307000.7:c.862T>A

ENST00000549247.6:n.636T>A

ENST00000551114.2:n.539T>A

ENST00000553106.5:c.877T>A

ENST00000635477.1:c.38T>A

NM_000277.2:c.877T>A

NM_001354304.1:c.877T>A

NM_000277.3:c.877T>A

NM_001354304.2:c.877T>A

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PS3_Supporting

PM3_Supporting

PP3

Evidence Links **3**

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.877T>A (p.Leu293Met) variant in PAH has been reported in 1 individual with classical PKU (BH4 deficiency excluded, detected with pathogenic variant IVS4-1G>A (PMID: 15503242). This variant is absent in population databases. Computational evidence support a deleterious effect (REVEL=0.742). In vitro PAH activity of L293M mutant is 41% of wild type (PMID: 16253218). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_moderate, PM2_supporting, PM3_supporting, PS3_supporting, PP3.

Met criteria codes

PM2_Supporting			Absent from gnomAD v2.1.1
PP4_Moderate			<div>L293M found in 1 patient with classical PKU. Urinary pterin analysis and dihydropteridine reductase (DHPR) assay were performed to exclude 6-pyruvoyl- tetrahydropterin synthase (PTPS) deficiencies. PMID: 15503242</div> <div>Patient 35: Genotype IVS4-1G>A/L293M, Classical PKU (1,200 uM or more). Urinary pterin analysis and dihydropteridine reductase (DHPR) assay were performed to exclude 6-pyruvoyl- tetrahydropterin synthase (PTPS) deficiencies. PubMed:15503242 </div>
PS3_Supporting			<div>In vitro PAH activity of L293M mutant is 41% PMID: 16253218</div> <div>96 PAH mutant alleles have been expressed to date in vitro in at least one expression system, and all were evaluated for inclusion in this study. L293M has 41% residual in vitro activity. PubMed:17924342 </div> <div>A transient protein overexpression system was used. The residual activities of mutant PAH enzymes were expressed as a percentage of the wild-type PAH enzyme activity and normalized to transfection efficiencies based on β-galactosidase activities. All the PAH mutants were transfected 3 times, enzyme activities were also measured 3 times, and the mean enzyme activities were calculated. L293M has 41% mean enzyme activity (range 15–81) PubMed:16253218 </div>
PM3_Supporting			<div>Detected with IVS4-1G>A (Pathogenic in ClinVar) When available, parental DNA samples were sequenced to confirm trans configurations in compound heterozygotes and to distinguish homozygosity from hemizygosity.</div> <div>L293M found in trans with IVS4-1G>A (VarID 594), Pathogenic in ClinVar PubMed:15503242 </div>
PP3			Tolerated in SIFT, deleterious in PolyPhen2, MutationTaster. REVEL=0.742.

Curation History



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