

Variant: *NM_000277.2(PAH):c.733G>A (p.Val245Met)*

Version: 1.0

CA229722 [↗](#)

102809 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: dd013c62-06e0-42a1-b503-4a26dfce4cf1

Approved on: 2020/11/10

Published on: 2022/2/20

HGVS expressions

NM_000277.2(PAH):c.733G>A (p.Val245Met)

NM_000277.2:c.733G>A

NC_000012.12:g.102852924C>T

CM000674.2:g.102852924C>T

NC_000012.11:g.103246702C>T

CM000674.1:g.103246702C>T

NC_000012.10:g.101770832C>T

NG_008690.1:g.69679G>A

NG_008690.2:g.110487G>A

ENST00000553106.6:c.733G>A

ENST00000307000.7:c.718G>A

ENST00000549247.6:n.492G>A

ENST00000553106.5:c.733G>A

NM_000277.1:c.733G>A

NM_001354304.1:c.733G>A

NM_000277.3:c.733G>A

NM_001354304.2:c.733G>A

Pathogenic

Met criteria codes **5**

PP3

PP4

PM2

PM5

PM3_Strong

Not Met criteria codes **1**

PS3

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.733G>A (p.Val245Met) variant in PAH has been reported in 2 individuals with PAH deficiency, detected in trans with pathogenic variants p.E178G (PMID: 26542770) and c.913-7A>G (PMID: 29316886). This variant is absent in population databases. Other missense variants at this same amino acid are interpreted as pathogenic (p.V245A, p.V245L, p.V245E). Computational prediction tools and

conservation analysis support a deleterious effect. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP4, PP3.

Met criteria codes

PP3			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.942.
PP4			<div>V245M seen in 1 patient with MHP. BH4 deficiency not ruled out.</div> <div>We included 376 PKU patients from 362 unrelated Danish families, representing all PKU patients in Denmark from 1967–2014 referred to the National Center for PKU. All patients had PKU according to biochemical criteria. C.733G>A seen in Patient 7 with MHP (210 umol/l serum Phe). PubMed:26542770 </div>
PM2			Absent from ExAC, gnomAD, 1000G, ESP.
PM5			V245L (varID 102810, Pathogenic 3 submitters), V245A Pathogenic- 10 submitters, V245E Pathogenic - 1 submitter/Invitae,
PM3_Strong			<div>V245M detected in trans with E178G (pathogenic) Parental testing confirmed PMID: 26542770; c.913-7A>G (P/LP by multiple submitters) variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 29316886</div> <div>V245M detected in trans with c.532G>A, p.E178G (VarID 92746, Pathogenic). Parental testing confirmed that the two mutations identified in the 368 patients all were present in trans. PubMed:26542770 </div>

Not Met criteria codes

PS3			p.Val245Met did not affect mRNA transcription in the eukaryotic expression system (HEK293T cells), however, mutant PAH proteins were markedly decreased in both prokaryotic (E. coli) and eukaryotic expression system. Protein activity not assessed, only expression. PMID: 29653233
-----	--	---	--

Curation History

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

[ClinGen Terms of Use.](#)

[⌕ Powered by BCM's Genboree.](#)