

Variant: *NM_000277.2(PAH):c.737C>T (p.Ala246Val)*

Version: 2.0

CA229727 [↗](#)

102813 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 160d0bef-780b-4613-8966-ecf9eb1ffef0

Approved on: 2024/9/6

Published on: 2024/9/6

HGVS expressions

NM_000277.2(PAH):c.737C>T (p.Ala246Val)

NM_000277.2:c.737C>T

NC_000012.12:g.102852920G>A

CM000674.2:g.102852920G>A

NC_000012.11:g.103246698G>A

CM000674.1:g.103246698G>A

NC_000012.10:g.101770828G>A

NG_008690.1:g.69683C>T

NG_008690.2:g.110491C>T

ENST00000553106.6:c.737C>T

ENST00000307000.7:c.722C>T

ENST00000549247.6:n.496C>T

ENST00000553106.5:c.737C>T

NM_000277.1:c.737C>T

NM_001354304.1:c.737C>T

NM_000277.3:c.737C>T

NM_001354304.2:c.737C>T

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PP3_Moderate

PP4_Moderate

PM3_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

The c.737C>T (p.Ala246Val) variant in PAH is a missense variant that is predicted damaging by REVEL (REVEL score 0.932) (PP3_Moderate). has been reported in multiple patients with PAH deficiency (BH4 deficiency excluded in one patient) (PMID: 9634518, 10394930, 12655553, 30747360, 32668217), including in one patient in unknown phase with the known pathogenic variant p.Arg408Trp (ClinVar ID: 577) (PM3_Supporting). The maximum population allele frequency in gnomAD v2.1.1 is 0.000008808, under the 0.0002 cutoff for use of PM2 (PM2_Supporting). 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, PM3_Supporting, PP3_Moderate, PP4_Moderate.

Met criteria codes

PM2_Supporting			The maximum population frequency in gnomAD is 0.000008808, <0.0002 cutoff for use of PM2
PP3_Moderate			REVEL=0.932
PP4_Moderate			A246V seen in 1 patient with mild PKU from Germany. PMID: 9634518, PMID: 10394930, PMID: 12655553. Also reported in a patient from China with MHP (All patients were excluded from tetrahydrobiopterin deficiency through a BH4 loading test, a urinary pterin analysis, and a DHPR activity assay on DBS samples) PMID: 30747360
PM3_Supporting			PMID: 32668217: 1 case, genotype p.Arg408Trp /p.Ala246Val, phase unconfirmed. The p.Arg408Trp variant is path in ClinVar by PAH VCEP (ID: 577)

Not Met criteria codes

PM5			A246D is interpreted as VUS by PAH VCEP (ClinVar ID 102812)
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Curation History

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