

Variant: *NM_000277.3(PAH):c.938C>T (p.Ala313Val)*

Version: 1.0

CA229861 [↗](#)

102903 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0a96804f-a9d8-44e3-aa66-b85b0dbe231d

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HGVS expressions

NM_000277.3(PAH):c.938C>T (p.Ala313Val)

NM_000277.3:c.938C>T

NC_000012.12:g.102846926G>A

CM000674.2:g.102846926G>A

NC_000012.11:g.103240704G>A

CM000674.1:g.103240704G>A

NC_000012.10:g.101764834G>A

NG_008690.1:g.75677C>T

NG_008690.2:g.116485C>T

ENST00000553106.6:c.938C>T

ENST00000307000.7:c.923C>T

ENST00000549247.6:n.697C>T

ENST00000551114.2:n.600C>T

ENST00000553106.5:c.938C>T

ENST00000635477.1:c.74-2495C>T

ENST00000635528.1:n.453C>T

NM_000277.1:c.938C>T

NM_000277.2:c.938C>T

NM_001354304.1:c.938C>T

NM_001354304.2:c.938C>T

Pathogenic

Met criteria codes **5**

PP4_Moderate PS3_Supporting

PM3_Strong PP3_Moderate

PM2_Supporting

Not Met criteria codes **3**

BP4 BS3 PM5

Evidence Links **0**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The NM_000277.3:c.938C>T variant in PAH is a missense variant predicted to cause substitution of alanine by valine at amino acid 313 (p.Ala313Val). This variant has been detected in at least 8 unrelated individuals with PAH deficiency (PMID: 32668217, PMID: 27121329, PMID: 33465300, PMID: 10234516, PMID: 23500595). Of these individuals, 6 were compound heterozygotes for the variant and pathogenic variants, p.Ala104Asp, c.1066-11G>A, p.Arg408Trp, p.Ex5del4232ins268, p.Gln267Ter, in unknown phase (PMID: 32668217, PMID: 27121329, PMID: 33465300) (3pts total, PM3_Strong). Of these individuals, two had plasma phenylalanine >120 µmol/L with the exclusion of a defect of BH4 cofactor metabolism (PP4_Moderate) (PMID: 10234516, PMID: 23500595). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). In a PAH enzyme assay, this variant showed 32% (<50%) of wild-type PAH enzyme activity (PMID: 18590700) (PS3_Supporting). The computational predictor REVEL gives a score of 0.907 which is above the threshold of 0.75, evidence that correlates with impact to PAH function (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID: 102903, 1 star review status) with one submitter classifying the variant as pathogenic and one submitter classifying the variant as a variant of uncertain significance. In summary, this variant meets the criteria to be classified as pathogenic for PAH deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen PAH Variant Curation Expert Panel (Specifications Version 2.0): PS3_Supporting, PM2_Supporting, PM3_Strong, PP3_Moderate, PP4.

Met criteria codes

PP4_Moderate			Of these individuals, two had plasma phenylalanine >120 µmol/L with the exclusion of a defect of BH4 cofactor metabolism (PP4_Moderate) (PMID: 10234516, PMID: 23500595).
PS3_Supporting			PMID: 18590700: in COS-1 cell system, variant showed 32% (<50%) of wild-type PAH enzyme activity
PM3_Strong			This variant has been detected in at least 8 unrelated individuals with PAH deficiency (PMID: 32668217, PMID: 27121329, PMID: 33465300, PMID: 10234516, PMID: 23500595). Of these individuals, 6 were compound heterozygotes for the variant and pathogenic variants, p.Ala104Asp, c.1066-11G>A, p.Arg408Trp, p.Ex5del4232ins268, p.Gln267Ter, in unknown phase (PMID: 32668217, PMID: 27121329, PMID: 33465300) (3pts total, PM3_Strong).
PP3_Moderate			The computational predictor REVEL gives a score of 0.907 which is above the threshold of 0.75, evidence that correlates with impact to PAH function (PP3_Moderate).
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

BP4			All predictors suggest damaging effect. REVEL =0.907
BS3			Mutation ID#11 with residual enzyme activity 32%
PM5			Both path/likely path and VUS reported at same amino acid residue: c.937G>A (p.Ala313Thr) is VUS in ClinVar; c.938C>A (p.Ala313Glu) is likely path (1 submitter); c.937G>C (p.Ala313Pro) is path (1 submitter)











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