

Variant: NM_000277.1(PAH):c.1208C>T (p.Ala403Val)

CA273106 [↗](#)

92731 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e8a0e1ef-d616-4dfe-a24e-30a901afa80f

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HGVS expressions

NM_000277.1:c.1208C>T

NM_000277.1(PAH):c.1208C>T (p.Ala403Val)

NC_000012.12:g.102840507G>A

CM000674.2:g.102840507G>A

NC_000012.11:g.103234285G>A

CM000674.1:g.103234285G>A

NC_000012.10:g.101758415G>A

NG_008690.1:g.82096C>T

NG_008690.2:g.122904C>T

NM_000277.2:c.1208C>T

NM_001354304.1:c.1208C>T

NM_000277.3:c.1208C>T

ENST00000307000.7:c.1193C>T

ENST00000551114.2:n.870C>T

ENST00000553106.5:c.1208C>T

ENST00000635477.1:n.312C>T

ENST00000635528.1:n.723C>T

Pathogenic

Met criteria codes **3**

PS3

PM3_Very Strong

PP4_Moderate

Not Met criteria codes **3**

PP3

PM5

PM2

Evidence Links **3**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PP4_Moderate: Seen on 3 PKU alleles, BH4 deficiency was ruled out. Upgraded per ClinGen Metabolic WG. (PMID:8268925); PM3_VeryStrong: A403V found with 4 pathogenic variants . Upgraded per ClinGen SVI workgroup. (PMID:9429153); PS3: In vitro A403V mutant protein activity was ~43% wt. (PMID:21820508). In summary this variant meets criteria to be

classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PP4_Moderate, PM3_VeryStrong, PS3).

Met criteria codes

PS3		In vitro A403V mutant protein activity was ~43% wt.
		We reproduced a full-length wild-type protein and seven natural full-length PAH variants (p.A403V), and analyzed their biochemical and biophysical behavior. The residual activity of the mutant PAH enzyme, expressed as a percentage of wild-type enzyme activity, was 43± 4% (p.A403V). Using confocal microscopy with the number and brightness technique, we studied the effect of BH4 addition directly in living human cells expressing wild-type PAH or p.A403V. Our results demonstrate that BH4 addition promotes re-establishment of the oligomerization equilibrium, thus indicating that the dimer-to-tetramer shift in pA403V plays a key role in BH4 responsiveness. PubMed:21820508
PM3_Very Strong		A403V found with 4 pathogenic variants . Upgraded per ClinGen SVI workgroup.
		A403V found in 13 Polish patients in trans with 4 different known pathogenic variants. R408W, R158Q, P281L, IVS10. PubMed:9429153
PP4_Moderate		Seen on 3 PKU alleles, BH4 deficiency was ruled out. Upgraded per ClinGen Metabolic WG.
		53 patients with persistently elevated blood levels of phenylalanine who met the differential criteria for PAH deficiency. A403V was found on 3 alleles. All patients were presenting with blood phenylalanine levels persistently above 150 /umol/l, and diagnosis of PAH deficiency was made when other potential causes of hyperphenylalaninemia had been ruled out. The criteria for inclusion were: normal serum tyrosine, normal urinary excretion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. PubMed:8268925

Not Met criteria codes

PP3		Conflicting predictions: tolerated in SIFT, deleterious in PolyPhen2, MutationTaster
PM5		No other reported variants in this codon
PM2		MAF= 0.00502 in gnomAD

Curation History [↗](#)

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