

Variant: *NM_000277.2(PAH):c.1301C>A (p.Ala434Asp)*

Version: 1.0

CA229427 [↗](#)

102586 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: d30a56d8-d14c-492c-afea-2eaecad4b3f1

Approved on: 2023/12/30

Published on: 2023/12/30

HGVS expressions

NM_000277.2(PAH):c.1301C>A (p.Ala434Asp)

NM_000277.2:c.1301C>A

NC_000012.12:g.102840414G>T

CM000674.2:g.102840414G>T

NC_000012.11:g.103234192G>T

CM000674.1:g.103234192G>T

NC_000012.10:g.101758322G>T

NG_008690.1:g.82189C>A

NG_008690.2:g.122997C>A

ENST00000553106.6:c.1301C>A

ENST00000307000.7:c.1286C>A

ENST00000551114.2:n.963C>A

ENST00000553106.5:c.1301C>A

ENST00000635477.1:c.405C>A

ENST00000635528.1:n.816C>A

NM_000277.1:c.1301C>A

NM_001354304.1:c.1301C>A

NM_000277.3:c.1301C>A

NM_001354304.2:c.1301C>A

Pathogenic

Met criteria codes 5

PM2_Supporting

PS3_Supporting

PM3_Very Strong

PP4_Moderate

PP3

Not Met criteria codes 1

PM5

Evidence Links 3

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen PAH Expert Panel
Specifications to the ACMG/AMP Variant Interpretation
Guidelines Version 1

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1301C>A (p.Ala434Asp) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded). PMID: 16256386, 21147011). This variant is absent in population databases. Residual enzyme activity of the p.A434D mutant is 21.7% of wild type, and the formation and stability of the PAH protein was affected (PMID: 18247293). This variant was detected with pathogenic variants: p.R252Q, p.R243Q (PMID: 16256386); p.E390G, p.R261Q (PMID: 21147011); p.R243Q (3 patients); IVS4-1G>A (2 patients); p.E280K, p.R111X (PMID: 23932990). Multiple lines of computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PP4_Moderate, PS3_supporting, PM2_supporting, PP3.

Met criteria codes

PM2_Supporting			Absent from ExAC, gnomAD, 1000G, and ESP
PS3_Supporting			Residual enzyme activity of A434D mutant is 21.7% of wild type. A434D affected the formation and stability of the PAH protein. PMID: 18247293
The enzyme activity of the 4 mutants was assessed by using transient protein expression in mammalian cells. The effects of the 4 missense mutations on the protein structure were analyzed. (1) The residual enzyme activity expressed in vitro of G247S, E280G, P362T and A434D were 3.1%, 0.4%, 8.2% and 21.7% of the wild-type PAH respectively; A434D affected the formation and stability of the dimer and the tetramer of PAH. PubMed:18247293 			
PM3_Very Strong			A434D seen with known pathogenic variants R252Q, R243Q. parental analysis when available PMID: 16256386; p.E390G (P 9 submitters), p.R261Q (P 11 submitters) parental analysis not reported PMID: 21147011; R243Q (3 patients); IVS4-1G>A (2 patients, P 5 submitters); E280K (P 9 submitters), R111X (P 6 submitters) parental analysis not reported PMID: 23932990
A434D+Y356X (VarID 595, Pathogenic/Likely Pathogenic) in 1 mild PKU patient. R252Q (VARID 102824, Pathogenic) + A434D in 1 classical PKU patient. R243Q (VarID 591, Pathogenic) + A434D in 1 classical PKU patient. Maternal or paternal inheritance of mutations was determined particularly for patients with novel mutation when parental DNA was available. Family gene analysis accomplished for each of them has also confirmed that the allele was inherited from the parent who did not carry other PKU mutations. PubMed:16256386 			
PP4_Moderate			A434D seen in 5 patients with classical & mild PKU and PAH deficiency. BH4 deficiency was ruled out in 2 patients by assessment of PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 16256386, PMID: 21147011
185 patients with PAH deficiency in 185 independent families from Northern China are included in this study. PAH deficiency was diagnosed by conventional biochemical methods. A434D appears in 3 classical and mild PKU patients. PubMed:16256386  588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). A434D seen in 2 patients. PubMed:21147011 			
PP3			Deleterious effect predicted in SIFT, Polyphen2, MutationTaster, REVEL=0.966

Not Met criteria codes

PM5



Only variant in this codon

Curation History [↗](#)

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