

Variant: *NM_000277.2(PAH):c.168G>T (p.Glu56Asp)*

Version: 1.0

CA229459 [↗](#)

102610 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 5d55702e-1dc3-4256-8539-e31f1b076a73

Approved on: 2020/6/29

Published on: 2021/7/9

HGVS expressions

NM_000277.2:c.168G>T

NM_000277.2(PAH):c.168G>T (p.Glu56Asp)

NC_000012.12:g.102912791C>A

CM000674.2:g.102912791C>A

NC_000012.11:g.103306569C>A

CM000674.1:g.103306569C>A

NC_000012.10:g.101830699C>A

NG_008690.1:g.9812G>T

NG_008690.2:g.50620G>T

ENST00000553106.6:c.168G>T

ENST00000307000.7:c.153G>T

ENST00000546844.1:c.168G>T

ENST00000548677.2:n.255G>T

ENST00000548928.1:n.90G>T

ENST00000549111.5:n.264G>T

ENST00000550978.6:c.152G>T

ENST00000551337.5:c.168G>T

ENST00000551988.5:n.257G>T

ENST00000553106.5:c.168G>T

ENST00000635500.1:n.136G>T

NM_000277.1:c.168G>T

NM_001354304.1:c.168G>T

NM_000277.3:c.168G>T

NM_001354304.2:c.168G>T

Pathogenic

Met criteria codes **3**

PM3_Very Strong

PP4_Moderate

PM2

Not Met criteria codes **2**

PP3

PM5

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Phenylketonuria VCEP

The c.168G>T (p.Glu56Asp) variant in PAH has been reported in multiple individuals with mild and classic PKU (BH4 deficiency excluded) (PMID: 21147011, 23932990, 30050108). This variant is absent in population databases. This variant was detected with multiple pathogenic variants: R243Q (PMID: 8019568); R408W and T356X (PMID: 21147011); p.V399V, c.442-1G>A, p.I65T, p.R261Q (PMID: 30050108). Computational prediction tools and conservation analysis do not agree on the impact to the protein. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4_Moderate.

Met criteria codes

PM3_Very Strong			E56D detected with: R243Q (maternally inh, P, 11 submitters) PMID: 8019568; R408W and T356X, both pathogenic in ClinVar. Parental analysis not reported. PMID: 21147011; p.V399V (P 5 submitters), c.442-1G>A (P 4 submitters), p.I65T (P 11 submitters), p.R261Q (P 11 submitters). PMID: 30050108 The validation tests on parents were performed. 6 pts
			E56D seen in trans with p.Y356X in 1 patient, and p.R408W (VarID 577, Pathogenic) in another patient PubMed:21147011 
PP4_Moderate			E56D found on 2 alleles in 2 patients with classic PKU. BH4 deficiency excluded: Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). PMID: 21147011; Found in 1 Chinese patient with PAH deficiency, A defect in the synthesis or recycling of tetrahydrobiopterin was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PMID: 23932990
			588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). E56D found on 2 alleles in 2 patients, both with classic PKU. PubMed:21147011 
PM2			Absent from ExAC, gnomAD, 1000G, ESP

Not Met criteria codes

PP3			Conflicting predictions of pathogenicity: Benign in Polyphen2, deleterious in SIFT and MutationTaster
PM5			The current variant is the only variant found in this codon in ClinVar

▼

▼

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.