

Variant: *NM_000277.1:c.689T>C*

Version: 1.0

CA16020840 [↗](#)

557425 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 5c77b53c-39cf-4cb1-8003-f25232414e04

Approved on: 2020/8/7

Published on: 2021/9/26

HGVS expressions

NM_000277.1:c.689T>C

NC_000012.12:g.102855153A>G

CM000674.2:g.102855153A>G

NC_000012.11:g.103248931A>G

CM000674.1:g.103248931A>G

NC_000012.10:g.101773061A>G

NG_008690.1:g.67450T>C

NG_008690.2:g.108258T>C

ENST00000553106.6:c.689T>C

ENST00000307000.7:c.674T>C

ENST00000549111.5:n.785T>C

ENST00000553106.5:c.689T>C

NM_000277.2:c.689T>C

NM_001354304.1:c.689T>C

NM_000277.3:c.689T>C

NM_001354304.2:c.689T>C

Likely Pathogenic

Met criteria codes **4**

PM3_Strong

PP3

PM2

PP4_Moderate

Not Met criteria codes **1**

PM5

Evidence Links **1**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.689T>C (p.Val230Ala) variant in PAH has been reported in multiple individuals with MHP, mild PKU and classical PKU (BH4 deficiency excluded, PMID: 18299955, 29316886, 30747360). This variant is absent in population databases. This variant was detected with multiple pathogenic/likely pathogenic variants: p.V230I, p.A300S, and p.Arg243Gln (PMID: 29316886). Computational evidence supports a

deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PP3.

Met criteria codes

PM3_Strong			V230A detected with 2 known pathogenic variants (V230I, A300S) in 2 patients. Parental analysis not reported PMID: 18299955. Detected in trans with p.Arg243Gln (P 11 submitters) PMID: 29316886
			V230A found in trans with V230I (Var ID 102784, Pathogenic/LP) in 1 patient with MHP, and in trans with A300S (Var ID 92751, Pathogenic) in 1 patient with mild PKU. PubMed:18299955 
PP3			Predicted deleterious in SIFT, PolyPhen2, MutationTaster
PM2			Absent from ExAC, gnomAD, 1000G, ESP
PP4_Moderate			V230A found in 1 MHP patient and 1 mild PKU patient. BH4 deficiency not ruled out. PMID: 18299955 Also found in a patient with mHP (480) PMID: 29316886 and classical PKU (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
			180 DNA samples (360 independent alleles) were obtained from unrelated patients with PKU. V230A was found in 1 patient with MHP (plasma phenylalanine concentrations of less than 6.5 mg/dl on a normal diet), and 1 patient with mild PKU (plasma phenylalanine concentrations 6.5–10 mg/dl and tolerate 400–600 mg/day of dietary phenylalanine). PubMed:18299955 

Not Met criteria codes

PM5			V230I (VarID 102784I is LP by PAH VCEP
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Curation History



 

 

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