

Variant: *NM_000277.2(PAH):c.699C>A (p.Phe233Leu)*

Version: 1.0

CA229699 [↗](#)

102790 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 334dab92-e6af-4ddc-84fb-6dd73004c37f

Approved on: 2020/11/9

Published on: 2022/2/20

HGVS expressions

NM_000277.2(PAH):c.699C>A (p.Phe233Leu)

NM_000277.2:c.699C>A

NC_000012.12:g.102855143G>T

CM000674.2:g.102855143G>T

NC_000012.11:g.103248921G>T

CM000674.1:g.103248921G>T

NC_000012.10:g.101773051G>T

NG_008690.1:g.67460C>A

NG_008690.2:g.108268C>A

ENST00000553106.6:c.699C>A

ENST00000307000.7:c.684C>A

ENST00000549111.5:n.795C>A

ENST00000553106.5:c.699C>A

NM_000277.1:c.699C>A

NM_001354304.1:c.699C>A

NM_000277.3:c.699C>A

NM_001354304.2:c.699C>A

Pathogenic

Met criteria codes **5**

PM3_Strong

PP4_Moderate

PP3

PM2

PM5

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.699C>A (p.Phe233Leu) variant in PAH has been reported in multiple individuals with PKU (BH4 deficiency excluded), detected in trans with pathogenic variants: p.S70del (PMID: 24705691); p.Ala403Val, p.Arg243Gln (PMID: 23500595). This variant is absent in population databases. Computational prediction tools and conservation analysis support a deleterious effect. Another variant at the same amino acid (p.F233I) is interpreted as pathogenic by the ClinGen PAH VCEP. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP4_Moderate, PP3.

Met criteria codes		
PM3_Strong	 	Detected in trans with S70del (Pathogenic in ClinVar). PMID: 24705691; p.Ala403Val (P), p.Arg243Gln (P) with p.Phe233Leu (c.699C>A). variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 29316886 3.0 pts Patient 11 Genotype: c.699C>A, F233L (maternally inherited)/ p.S70del (paternally inherited) PubMed:24705691
PP4_Moderate	 	F233L seen on 4 PKU alleles. PTPS deficiency excluded in 1 patient (PAH, PTS, GCH1, QDPR, PCBD1 and GFRP genes, including 50 bp in the intron-exon boundaries were directly sequenced). PMID: 24705691 PKU patients from four centers in three countries of Great Britain were studied. 490 independent mutant chromosomes were analyzed. F233L was seen on 3 PKU alleles. PubMed:9012412 The cohort study consisted of 93 subjects from 32 families, including 33 patients diagnosed with PKU and two patients diagnosed with BH4 deficiency according to the diagnostic criteria published in Blau et al., 2011. the 39 exons of PAH, PTS, GCH1, QDPR, PCBD1 and GFRP genes, including 50 bp in the intron-exon boundaries were directly sequenced. c.699C>A (F233L) was seen in patient 11 with mild HPA. PubMed:24705691
PP3	 	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.904
PM2		Absent from ExAC, gnomAD, 1000G, ESP
PM5	 	p.F233I interpreted as pathogenic by 1 submitter (PAH VCEP: PP4_Moderate, PS3, PM3_strong, PM2, PP3)

Curation History 
Showing 1 to 1 of 1 rows