The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.2(PAH):c.799C>G (p.Gln267Glu)

CA229769

102839 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3cf6d080-cff7-4ce2-9226-e050a058efd5
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HGVS expressions

NM_000277.2(PAH):c.799C>G (p.Gln267Glu)
NM_000277.2:c.799C>G
NC_000012.12:g.102852858G>C
CM000674.2:g.102852858G>C
NC_000012.11:g.103246636G>C
CM000674.1:g.103246636G>C
NC_000012.10:g.101770766G>C
NG_008690.1:g.69745C>G
NG_008690.2:g.110553C>G
NM_000277.1:c.799C>G
NM_001354304.1:c.799C>G
NM_000277.3:c.799C>G
ENST00000307000.7:c.784C>G
ENST00000549247.6:n.558C>G
ENST00000553106.5:c.799C>G

Pathogenic

Met criteria codes 5

PS3 PP3 PP4 PM2 PM3

Not Met criteria codes 1

PM5

Evidence Links 4

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.799C>G (p.Gln267Glu) variant in PAH was reported in 2 Chinese PKU patients. BH4 deficiencies not completely ruled out. (PMID: 26600521) This variant was detected with known pathogenic variants p.R111X (PMID: 16256386), and D101N (not in ClinVar, PMID: 26600521). It is absent from ExAC, gnomAD, 1000G, and ESP. This variant is predicted deleterious in SIFT, Polyphen2, MutationTaster, and REVEL=0.935. This variant was expressed in e. coli using a rat Q267E mutant. It has 11% activity of wt. based on duplicate determinations

of a single clone. (PMID: 7914195). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3, PS3, PP3, PP4.

Met criteria codes

PS3 ✔

Rat Q267E mutant has 11% activity of wt. expressed in e. coli. Duplicate determinations of a single clone. PMID: 7914195

Data on in vitro expression of 35 inherited human mutations and 22 created rat mutations are reviewed. The core data are accessible at the PAH Mutation Analysis Consortium Web site (http://www.mcgill.ca/pahdb). Q267E expressed in E. coli JPA-101, 11 Spec. act. with BH4 as % of wt. Dickson et al., 1994. PubMed:9450897
Rat phenylalanine hydroxylase was expressed in Escherichia coli. The E. coli expression system was used to generate a number of mutations in phenylalanine hydroxylase from position 264 to 290. Purified mutant PAH activities were the average of duplicate determinations of a single clone. Q267E expressed in E. coli JPA-101, 11% Spec. act. as % of wt. PubMed:7914195

PP3 ✔

Predicted deleterious in SIFT, Polyphen2, MutationTaster. REVEL=0.935

PP4 ✔

Q267E was detected in 2 Chinese PKU patients. BH4 deficiencies not completely ruled out. PMID: 26600521

Genomic DNA was extracted from the peripheral blood from members of 112 families and the exons and exon-intron boundaries of the PAH gene were amplified by PCR. All the probands in the research had abnormal blood phenylalanine (Phe) concentrations (>120 μM) and had differential diagnosis detected by BH4-loading test, excluding BH4 deficiency. Q267E was found in family 86. PubMed:26600521
By using PCR/SSCP and DNA sequencing, all exons of PAH gene in the 185 unrelated patients with PKU from Northern China were studied. Fifteen novel mutations were identified in this study, including Q267H, Q267E. Each of them occurs at very low frequency (0.3-1.1%). PubMed:16256386

PM2 ✔

Absent from ExAC, gnomAD, 1000G, ESP

PM3 ✔

Detected with R111X (PMID: 16256386), and D101N (not in ClinVar, PMID: 26600521).

Proband genotype: D101N (paternal)/Q267E (Maternal). PubMed:26600521
Patient genotype: Q267E + R111X (VarID 581, Pathogenic). Maternal or paternal inheritance of mutations was determined particularly for patients with novel mutation when parental DNA was available. PubMed:16256386

Not Met criteria codes

PM5 ✖

2 other variants reported in ClinVar at this aa. Q267L is likely pathogenic.

Curation History

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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.