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_000277.3:c.659A>C

Version: 1.0

CA16020832

932276 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: dd2f6143-fa77-4772-babc-2d24929caa57
Approved on: 2020/3/8
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HGVS expressions

NM_000277.3:c.659A>C
NC_000012.12:g.102855183T>G
CM000674.2:g.102855183T>G
NC_000012.11:g.103248961T>G
CM000674.1:g.103248961T>G
NC_000012.10:g.101773091T>G
NG_008690.1:g.67420A>C
NG_008690.2:g.108228A>C
ENST00000553106.6:c.659A>C
ENST00000307000.7:c.644A>C
ENST00000549111.5:n.755A>C
ENST00000553106.5:c.659A>C
NM_000277.1:c.659A>C
NM_000277.2:c.659A>C
NM_001354304.1:c.659A>C
NM_001354304.2:c.659A>C

Likely Pathogenic

Met criteria codes 3

PP4_Moderate PM3_Strong PM2

Not Met criteria codes 1

PP3

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.659A>C (p.His220Pro) variant in PAH has been reported in 3 individuals with MHP or classic PKU (BH4 deficiency excluded, PMID 26322415) detected in trans with pathogenic variant p.R241C in 2 patients (PMID: 30050108). This variant is absent in population databases. Computational evidence is conflicting. 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.

Met criteria codes

PP4_Moderate	✔	PMID 26322415: listed p.[A156P];[H220P] in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded byanalysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PMID 26322415: listed p.[A156P];[H220P] in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded byanalysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415
PM3_Strong	✔	PMID 26322415: detected with p.[A156P] no interpretation in ClinVar and p.R241C (P 8 submitters, 2 patients) PMID: 30050108. All mutations identified in patients were confirmed by analyzing parental DNA. When mutation loci were detected in patients, the same locus of the parental sample was amplified by PCR and analyzed by Sanger automated sequencing. PubMed:30050108 PMID 26322415: listed p.[A156P];[H220P] in one patient with classic PKU (Phe levels >20mg/dl). All patients fulfilled the diagnostic criteria of PKU, with a blood phenylalanine concentration >2mg/dl. BH4 deficiency was excluded byanalysis of urinary pterins and dihydropteridine reductase activity in erythrocytes. PubMed:26322415
PM2	✔	Absent from controls in ExAC, gnomAD, 1000 Genomes, or ESP

Not Met criteria codes

PP3	✖	Conflicting predictions

Curation History

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