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_000277.1(PAH):c.782G>C (p.Arg261Pro)

Version: 1.0

CA229759

102832 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e50d8620-443e-4dd4-949e-81a67d4b702d
Approved on: 2019/8/11
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HGVS expressions

NM_000277.1:c.782G>C
NM_000277.1(PAH):c.782G>C (p.Arg261Pro)
NC_000012.12:g.102852875C>G
CM000674.2:g.102852875C>G
NC_000012.11:g.103246653C>G
CM000674.1:g.103246653C>G
NC_000012.10:g.101770783C>G
NG_008690.1:g.69728G>C
NG_008690.2:g.110536G>C
ENST00000553106.6:c.782G>C
ENST00000307000.7:c.767G>C
ENST00000549247.6:n.541G>C
ENST00000553106.5:c.782G>C
NM_000277.2:c.782G>C
NM_001354304.1:c.782G>C
NM_000277.3:c.782G>C
NM_001354304.2:c.782G>C

Pathogenic

Met criteria codes 5

PP3 PP4 PM5 PM2 PM3_Strong

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The PAH c.782G>C (p.Arg261Pro) variant has been reported in multiple affected individuals (PMID: 26666653, Bh4 deficiency not ruled out, PP4). It has been detected with 5 known pathogenic variants (PM3_S). It is absent from ExAC/gnomAD. Computational evidence supports a deleterious effect. Also, p.R261Q is interpreted as pathogenic. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_S, PM2, PM5, PP4, PP3.

Met criteria codes

PP3	✔	Multiple lines of computational evidence support a deleterious effect (SIFT, Polyphen2, MutationTaster, REVEL=0.978)
PP4	✔	Detected in 5 patients with PKU (PMID: 26666653). BH4 deficiency not ruled out. Table1_p. [Ile65Thr]; [Arg261Pro]_pt has classic PKU and Total BH4 loading test not responding. ['According to their blood Phenylalanine concentration at time of diagnosis, these patients were assigned to one of the three phenotype categories: mild hyperphenylalaninemia (mHP, 180 < Phe < 600 µmol/L); mild phenylketonuria (mPKU, 600 < Phe < 1200 µmol/L) and classical phenylketonuria (cPKU, Phe > 1200 µmol/L).'] PubMed:26666653
PM5	✔	R261Q is PATH
PM2	✔	Not seen in ExAC, gnomAD. low frequency in 1000G and PAGE
PM3_Strong	✔	Detected with 5 known pathogenic variants PMID: 26666653, Parental analysis not reported. 2.5 points = PM3 strong Table1: p. [Ile65Thr] (Pathogenic in ClinVar;VarID 636); [Arg261Pro]. p. [Arg158Trp]; [Arg261Pro]. p. [Arg261Gln]; [Arg261Pro]. p. [Arg261Pro]; [Tyr414Cys]. c. [782G > C]; [1315 + 1G > A]. Parental analysis not reported. PubMed:26666653

Curation History

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