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.830A>G (p.Tyr277Cys)

Version: 1.0

CA229800

102860 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 159e0913-0a8e-4eef-9a1d-2cd35121aaca
Approved on: 2020/6/8
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HGVS expressions

NM_000277.2:c.830A>G
NM_000277.2(PAH):c.830A>G (p.Tyr277Cys)
NC_000012.12:g.102852827T>C
CM000674.2:g.102852827T>C
NC_000012.11:g.103246605T>C
CM000674.1:g.103246605T>C
NC_000012.10:g.101770735T>C
NG_008690.1:g.69776A>G
NG_008690.2:g.110584A>G
ENST00000553106.6:c.830A>G
ENST00000307000.7:c.815A>G
ENST00000549247.6:n.589A>G
ENST00000553106.5:c.830A>G
NM_000277.1:c.830A>G
NM_001354304.1:c.830A>G
NM_000277.3:c.830A>G
NM_001354304.2:c.830A>G

Pathogenic

Met criteria codes 5

PM2 PM5 PP3 PP4 PM3_Strong

Not Met criteria codes 1

BP2

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.830A>G (p.Tyr277Cys) variant in PAH has been reported in multiple individuals with PKU (PMID:24350308). This variant has an extremely low allele frequency (MAF=0.00006) in gnomAD. It was detected with multiple pathogenic variants: p.R408W in 2 patients; p.L194P (PMID: 24350308); c.842+1G>A in 2 patients (PMID: 25952249). Computational prediction tools and conservation analysis support

a deleterious effect. Another missense change at the same amino acid (p.Y277D), is pathogenic by 8 submitters. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP3, PP4

Met criteria codes

PM2	✔	Low freq found in gnomAD (MAF=0.00006) Absent in 1000 Genomes and ESP.
PM5	✔	Y277D, pathogenic in Clinvar (Var ID=603) 8 submitters
PP3	✔	Predicted deleterious by MutationTaster, Polyphen, and SIFT.
PP4	✔	Found in 3 individuals with PKU. BH4 deficiency not reportedly ruled out. PMID: 24350308
		Found in individual with PKU but in cis with V245A and in trans with IVS12+1G>A. PubMed:16601866
PM3_Strong	✔	detected with p.R408W (P 14 submitters) in 2 patients; p.L194P(c.581T>C) LP PAH VCEP parental analysis not reported PMID: 24350308; c.842+1G>A in 2 patients (P 3 submitters) PMID: 25952249 parental analysis not reported 2.25 pts

Not Met criteria codes

BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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