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:c.833C>G

Version: 1.0

CA16020867

932254 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: d2e319bb-303f-4130-b819-df9e61745387
Approved on: 2020/6/15
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HGVS expressions

NM_000277.1:c.833C>G
NC_000012.12:g.102852824G>C
CM000674.2:g.102852824G>C
NC_000012.11:g.103246602G>C
CM000674.1:g.103246602G>C
NC_000012.10:g.101770732G>C
NG_008690.1:g.69779C>G
NG_008690.2:g.110587C>G
ENST00000553106.6:c.833C>G
ENST00000307000.7:c.818C>G
ENST00000549247.6:n.592C>G
ENST00000553106.5:c.833C>G
NM_000277.2:c.833C>G
NM_001354304.1:c.833C>G
NM_000277.3:c.833C>G
NM_001354304.2:c.833C>G

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PM2 PM5 PP4_Moderate

Not Met criteria codes 1

PP3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.833C>G (p.Thr278Ser) variant in PAH has been reported in 1 individual with mild PKU (BH4 deficiency excluded), detected with pathogenic variant IVS4-1G>A (PMID: 15503242). This variant is absent in population databases. Computational evidence is conflicting. There is another missense variant at the same amino acid that is interpreted as pathogenic (p.T278I, Variant ID:102863). In summary, this

variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_supporting, PM5.

Met criteria codes

PM3_Supporting	✔	detected with IVS4-1G>A (pathogenic in Clinvar). When available, parental DNA samples were sequenced to confirm trans configurations in compound heterozygotes and to distinguish homozygosity from hemizygosity. PMID: 15503242 Found in trans with IVS4 (Variant ID 594) which is pathogenic in Clinvar. PubMed:15503242
PM2	✔	Absent from controls in ExAC, 1000 Genomes, ESP, and gnomAD.
PM5	✔	T278I (Variant ID:102863), interpreted as pathogenic by 2 submitters
PP4_Moderate	✔	Found in individual with classic PKU on exon 7. Urinary pterin analysis and dihydropteridine reductase (DHPR) assay were performed to exclude 6-pyruvoyltetrahydropterin synthase (PTPS) deficiencies. PMID: 15503242 Found in individual with classic PKU on exon 7. PTPS deficiency ruled out. PubMed:15503242

Not Met criteria codes

PP3	✖	Tolerated in SIFT. Predicted deleterious in PolyPhen and MutationTaster.

Curation History

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