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.803A>G

CA16020863

619165 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 547677d3-f246-4f3d-9f34-55a803c2335a
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HGVS expressions

NM_000277.1:c.803A>G
NC_000012.12:g.102852854T>C
CM000674.2:g.102852854T>C
NC_000012.11:g.103246632T>C
CM000674.1:g.103246632T>C
NC_000012.10:g.101770762T>C
NG_008690.1:g.69749A>G
NG_008690.2:g.110557A>G
NM_000277.2:c.803A>G
NM_001354304.1:c.803A>G
NM_000277.3:c.803A>G
ENST00000307000.7:c.788A>G
ENST00000549247.6:n.562A>G
ENST00000553106.5:c.803A>G

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PM2 PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.803A>G (p.Tyr268Cys) variant in PAH has been reported in 1 individual with hyperphenylalaninemia (BH4 deficiency excluded) and was detected with pathogenic variant p.Glu178Gly. (PP4_Moderate, PM3; PMID: 26481238). This variant is absent in population databases (PM2). Computational evidence support a deleterious effect (PP3). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3, PP3.

Met criteria codes

PP3		✔	Deleterious effect predicted in SIFT, Polyphen2, MutationTaster. REVEL=0.962
PM3		✔	Detected with Glu178Gly, pathogenic in ClinVar.
			Y268C seen with Glu178Gly (VarID 92746, Pathogenic). PubMed:26481238
PM2		✔	Absent from ExAC, gnomAD, 1000G, ESP.
PP4_Moderate		✔	Y268C seen in a Romanian hyperphenylalaninemia patient. BH4 deficiency assessed. PMID: 26481238
			Investigated the mutation spectrum for the PAH gene in a cohort of 81 PKU patients from Romania and found two new missense mutations, p.Gln226Lys and p.Tyr268Cys. Pterin concentrations were measured from dried blood spots using a HPLC method for pterins. DHPR activity was measured from dried blood spots by enzyme assay. Case F9C had Y268C, with a blood Phe level of 485 on newborn screening. PubMed:26481238

Not Met criteria codes

PM5		✖	1 other variant in this codon, VUS.

Curation History

Showing 1 to 1 of 1 rows

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