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Variant: NM_000277.2(PAH):c.823C>T (p.Pro275Ser)

CA229789

102853 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 85ea4e16-15ba-4de1-88b7-46e398122a6e
Approved on: 2018-12-09
Published on: 2018-12-10

HGVS expressions

NM_000277.2(PAH):c.823C>T (p.Pro275Ser)
NM_000277.2:c.823C>T
NC_000012.12:g.102852834G>A
CM000674.2:g.102852834G>A
NC_000012.11:g.103246612G>A
CM000674.1:g.103246612G>A
NC_000012.10:g.101770742G>A
NG_008690.1:g.69769C>T
NG_008690.2:g.110577C>T
NM_000277.1:c.823C>T
NM_001354304.1:c.823C>T
NM_000277.3:c.823C>T
ENST00000307000.7:c.808C>T
ENST00000549247.6:n.582C>T
ENST00000553106.5:c.823C>T

Pathogenic

Met criteria codes 5

PP3 PM5 PM2 PM3_Strong PP4_Moderate

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.823C>T (p.Pro275Ser) variant in PAH is absent from all population databases, and is in the same codon as two other likely pathogenic variants. In silico algorithms agree on a damaging effect. It has been identified in trans with two independent pathogenic variants (R408W and c.669delC; PMID: 20123475, 24705691), and a defect in BH4 metabolism was excluded as a cause of elevated phenylalanine in multiple patients. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PP4_Moderate, PM5, PP3.

Met criteria codes

PP3	✔	In silico agree damaging. REVEL=0.954
PM5	✔	p.Pro275Leu and p.Pro275Arg, both LP in ClinVar
PM2	✔	not found in any population databases
PM3_Strong	✔	R408W (Cassio, 2010) c.669delC (Gu, 2014) in trans with c.669delC **PubMed:24705691** in trans with R408W **PubMed:20123475**
PP4_Moderate	✔	BH4 defect excluded in all patients (PMID: 24705691, PMID: 20123475). Phe = 380umol/L (Gassio 2010) BH4 defect excluded in all patients **PubMed:24705691** BH4 defect excluded in all patients **PubMed:20123475**

Curation History

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