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Variant: NM_000277.2(PAH):c.848T>A (p.Ile283Asn)

CA229821

102877 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: bff8b781-b702-44cc-bf6e-880d367c1a91
Approved on: 2018-12-09
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HGVS expressions

NM_000277.2:c.848T>A
NM_000277.2(PAH):c.848T>A (p.Ile283Asn)
NC_000012.12:g.102851751A>T
CM000674.2:g.102851751A>T
NC_000012.11:g.103245529A>T
CM000674.1:g.103245529A>T
NC_000012.10:g.101769659A>T
NG_008690.1:g.70852T>A
NG_008690.2:g.111660T>A
NM_000277.1:c.848T>A
NM_001354304.1:c.848T>A
NM_000277.3:c.848T>A
ENST00000307000.7:c.833T>A
ENST00000549247.6:n.607T>A
ENST00000551114.2:n.510T>A
ENST00000553106.5:c.848T>A
ENST00000635477.1:n.9T>A

Pathogenic

Met criteria codes 5

PM5 PM2 PM3_Strong PP3 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.848T>A (p.Ile283Asn) variant in PAH is absent from population databases and predicted damaging with in silico predictors. It is a novel missense change in a residue where a different pathogenic variant has been identified (c.847A>T (p.Ile283Phe). It has been identified in multiple affected individuals in trans with known pathogenic variants (PMID: 9521426, 26413448), and was identified in a patient in which a defect in BH4 metabolism had been excluded. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_strong, PM2, PM5, PP4_Moderate, PP3.

Met criteria codes

PM5	✔	NM_000277.2(PAH):c.847A>T (p.Ile283Phe) is LP/P
PM2	✔	Absent from pop databases
PM3_Strong	✔	2 patients in (PMID: 9521426), 1 with mild PKU in trans with Y414C and 1 with classic PKU in trans with c.1066-11>G, and 1 homozygous c.848T>A patient with classic PKU in Biglari, 2015 (PMID26413448)) 2 patients, 1 in trans with Y414C and 1 in trans with c.1066-11>G PubMed:9521426 Single patient, homozygous, with classic PKU PubMed:26413448
PP3	✔	All agree damaging effect REVEL=0.898
PP4_Moderate	✔	BH4 defect excluded in all patients (Bosco 1998 PMID 9521426)

Curation History

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