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_000277.3:c.902A>C

Version: 1.0

CA16020889

805825 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6b22f5b5-b654-4763-936d-fd132e4d0fbc
Approved on: 2019/7/14
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HGVS expressions

NM_000277.3:c.902A>C
NC_000012.12:g.102851697T>G
CM000674.2:g.102851697T>G
NC_000012.11:g.103245475T>G
CM000674.1:g.103245475T>G
NC_000012.10:g.101769605T>G
NG_008690.1:g.70906A>C
NG_008690.2:g.111714A>C
ENST00000553106.6:c.902A>C
ENST00000307000.7:c.887A>C
ENST00000549247.6:n.661A>C
ENST00000551114.2:n.564A>C
ENST00000553106.5:c.902A>C
ENST00000635477.1:c.63A>C
NM_000277.1:c.902A>C
NM_000277.2:c.902A>C
NM_001354304.1:c.902A>C
NM_001354304.2:c.902A>C

Pathogenic

Met criteria codes 5

PM2 PM3_Supporting PS3 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.902A>C (p.Gln301Pro) variant in PAH has been reported in at least 1 individual with hyperphenylalaninemia, who carried a second pathogenic variant (p.Leu48Ser) (BH4 deficiency ruled out, parental analysis not performed) (PMID: 19292873, 25757997) . The p.Gln301Pro variant is absent in gnomAD and the ESP population databases. A deleterious effect is predicted in SIFT, Polyphen-2, MutationTaster, and REVEL=0.987. In addition the p.Gln301Pro causes a significant reduction of enzyme activity and expression when

tested in vitro (PMID: 19292873). In summary, this variant meets the criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP3, PM2, PM3_supporting, PS3, PP4_moderate.

Met criteria codes

PM2	✔	absent from gnomAD
PM3_Supporting	✔	Detected in trans with pathogenic p.L48S. Parental analysis not reported. Detected in trans with pathogenic p.L48S (table 2). PubMed:19292873
PS3	✔	Figure 1b demonstrate loss of enzyme activity. 4% residual enzyme activity. Figure 1b demonstrate loss of enzyme activity: ~4% residual PubMed:19292873
PP3	✔	REVEL 0.987; Polyphen and SIFT damaging
PP4_Moderate	✔	Detected in a patient with HPA II. Pre-treatment Phe level 2117 uM. PMID: 19292873 BH4 deficiency excluded. PMID: 25757997 Detected in a patient with HPA II. Pre-treatment Phe level 2117 uM. PubMed:19292873 Same patient, Patients with concurrent diseases that would interfere with enrollment or safety, with concomitant drug treatment, with clinical diagnosis of primary BH4 deficiency or unavailable for study participation were excluded from the study. PubMed:25757997

Curation History

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