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(PAH):c.1241A>G (p.Tyr414Cys)

CA114362

593 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 52c5efc0-4153-4bd6-a94a-132ad01f1d73
Approved on: 2018-07-27
Published on: 2018-12-10

HGVS expressions

NM_000277.1:c.1241A>G
NM_000277.1(PAH):c.1241A>G (p.Tyr414Cys)
NC_000012.12:g.102840474T>C
CM000674.2:g.102840474T>C
NC_000012.11:g.103234252T>C
CM000674.1:g.103234252T>C
NC_000012.10:g.101758382T>C
NG_008690.1:g.82129A>G
NG_008690.2:g.122937A>G
NM_000277.2:c.1241A>G
NM_001354304.1:c.1241A>G
NM_000277.3:c.1241A>G
ENST00000307000.7:c.1226A>G
ENST00000551114.2:n.903A>G
ENST00000553106.5:c.1241A>G
ENST00000635477.1:n.345A>G
ENST00000635528.1:n.756A>G

Pathogenic

Met criteria codes 5

PP3 PM5 PP4_Moderate PM3_Very Strong PS3

Not Met criteria codes 1

PM2

Evidence Links 6

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

PAH-specific ACMG/AMP criteria applied: PM5: c.1240T>C likely pathogenic in ClinVar; PP3: All computational evidence supports deleterious effect. REVEL=0.982; PS3: 50% activity, 50% immunoreactivity (PMID:2044609); PM3_VeryStrong: Patient #41 p.R408W / p.Y414C, Phe 744 @dx and two homozygous individuals. Total of 9 patients with this variant (PMID:22526846; PMID:17935162;

PMID:9399896; PMID:21871829; PMID:26542770); PP4_Moderate: BH4 defect excluded in all patients (PMID:22526846). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PM5, PP3, PS3, PM3_VeryStrong, PP4_Moderate).

Met criteria codes

PP3	✔	All computational evidence supports deleterious effect. REVEL=0.982
PM5	✔	c.1240T>C likely pathogenic in ClinVar
PP4_Moderate	✔	BH4 defect excluded in all patients reported in 9 patients (2 homozygous). Both homozygous patients with Phe levels 300-400 (Mild Hyperphenylalanemia), other patients with variable Phe levels depending on 2nd variant. BH4 defect excluded in all patients** (PP4_strong-specific analyte with other biochemical causes ruled out) Patient #41 p.R408W / p.Y414C, Phe 744 @dx (PM3 (in trans with known pathogenic variant) PubMed:22526846
PM3_Very Strong	✔	Patient #41 p.R408W / p.Y414C, Phe 744 @dx and two homozygous individuals. Total of 9 patients with this variant compound het patients PubMed:21871829 compound het PubMed:26542770 compound het and homozygous patients PubMed:9399896 compound het patients PubMed:17935162 reported in 9 patients (2 homozygous). Both homozygous patients with Phe levels 300-400 (Mild Hyperphenylalanemia), other patients with variable Phe levels depending on 2nd variant. One paBH4 defect excluded in all patients** (PP4_strong-specific analyte with other biochemical causes ruled out) Patient #41 p.R408W / p.Y414C, Phe 744 @dx (PM3 (in trans with known pathogenic variant) PubMed:22526846
PS3	✔	50% activity, 50% immunoreactivity 50% activity, 50% immunoreactivity PubMed:2044609

Not Met criteria codes

PM2	✖	PAH specific PM2 criteria are <0.02% (AF=0.0002)

Curation History

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