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(PAH):c.1237C>A (p.Arg413Ser)

Version: 1.0

CA229411

102575 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8f012027-88de-4c03-965a-c6f579340b1d
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_000277.3:c.1237C>A
NM_000277.3(PAH):c.1237C>A (p.Arg413Ser)
NC_000012.12:g.102840478G>T
CM000674.2:g.102840478G>T
NC_000012.11:g.103234256G>T
CM000674.1:g.103234256G>T
NC_000012.10:g.101758386G>T
NG_008690.1:g.82125C>A
NG_008690.2:g.122933C>A
ENST00000553106.6:c.1237C>A
ENST00000307000.7:c.1222C>A
ENST00000551114.2:n.899C>A
ENST00000553106.5:c.1237C>A
ENST00000635477.1:c.341C>A
ENST00000635528.1:n.752C>A
NM_000277.1:c.1237C>A
NM_000277.2:c.1237C>A
NM_001354304.1:c.1237C>A
NM_001354304.2:c.1237C>A

Pathogenic

Met criteria codes 5

PM5 PP3_Strong PS3_Supporting PM2_Supporting PP4_Moderate

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Phenylketonuria Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for PAH Version 2.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1237C>A (p.Arg413Ser) variant in PAH has been reported in 1 patient with mild hyperphenylalenemia (BH4 deficiency excluded). This variant has been reported in at least 2 in vitro studies showing <50% PAH activity as compared to wild type. This variant is absent from population databases, and is predicted deleterious by SIFT, PolyPhen2, MutationTaster, REVEL = 0.934. This variant is at the same codon as c.1238G>C (p.Arg413Pro) which has been curated as pathogenic by the ClinGen PAH VCEP (ClinVarID:592). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3_supporting, PM2_supporting, PM5, PP4_Moderate, PP3_strong.

Met criteria codes

PM5	✔	c.1238G>C (p.Arg413Pro) has been curated as pathogenic by the ClinGen PAH VCEP (ClinVarID:592); c.1237C>G (p.Arg413Gly) - not reported in ClinVar; not yet curated by ClinGen PAH VCEP; c.1237C>T (p.Arg413Cys) curated by ClinGen PAH VCEP as VUS (VarID:102576)
PP3_Strong	✔	Predicted deleterious by SIFT, PolyPhen2, MutationTaster, REVEL = 0.934.
PS3_Supporting	✔	2 in vitro studies showing 32-34% PAH activity . PMID: 30037505, PMID: 10479481 20-40% enzyme activity, 12 variants tested, none benign **PubMed:10479481**
PM2_Supporting	✔	Variant absent from gnomAD v2.1.1
PP4_Moderate	✔	PMID: 9634518 - R413S detected in 1 patient with mild hyperphenylalenemia (Phe < 600 mmol/liter), BH4 deficiency excluded

Curation History

Showing 1 to 1 of 1 rows

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