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_001354304.2:c.395C>T

Version: 1.0

CA16020783

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: e8601430-64a6-442b-8bd1-e34f63c3068f
Approved on: 2024/9/6
Published on: 2024/9/6

HGVS expressions

NM_001354304.2:c.395C>T
NC_000012.12:g.102877508G>A
CM000674.2:g.102877508G>A
NC_000012.11:g.103271286G>A
CM000674.1:g.103271286G>A
NC_000012.10:g.101795416G>A
NG_008690.1:g.45095C>T
NG_008690.2:g.85903C>T
ENST00000553106.6:c.395C>T
ENST00000307000.7:c.380C>T
ENST00000549111.5:n.491C>T
ENST00000550978.6:c.379C>T
ENST00000551337.5:c.395C>T
ENST00000551988.5:n.484C>T
ENST00000553106.5:c.395C>T
NM_000277.1:c.395C>T
NM_000277.2:c.395C>T
NM_001354304.1:c.395C>T
NM_000277.3:c.395C>T

Likely Pathogenic

Met criteria codes 4

PP3_Moderate PP4_Moderate PM3_Supporting PM2_Supporting

Not Met criteria codes 1

PM5

Evidence Links 0

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.395C>T (p.Ala132Val) in PAH is reported in a Japanese patient with mild hyperphenylalaninemia (BH4 deficiency ruled out), detected with pathogenic variant p.Arg413Pro (PMID: 21307867). This variant is absent in population databases. Multiple lines of computational evidence support a deleterious effect (REVEL=0.878). In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2_supporting, PM3_supporting, PP3_moderate, PP4_moderate.

Met criteria codes

PP3_Moderate	✔	predicted deleterious in SIFT, PolyPhen-2, MutationTaster, REVEL=0.878
PP4_Moderate	✔	Reported in a Japanese patient with mild HPA, analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine PMID: 21307867
PM3_Supporting	✔	A132V/R413P (P), parental analysis not reported PMID: 21307867
PM2_Supporting	✔	absent from gnomAD

Not Met criteria codes

PM5	✖	no other missense change at this aa in ClinVar

Curation History

Showing 1 to 1 of 1 rows

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