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:c.1301C>T

Version: 1.0

CA16020990

1327550 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: aa9f120b-6559-4c5b-9976-8f1c79750adc
Approved on: 2020/8/13
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HGVS expressions

NM_000277.1:c.1301C>T
NC_000012.12:g.102840414G>A
CM000674.2:g.102840414G>A
NC_000012.11:g.103234192G>A
CM000674.1:g.103234192G>A
NC_000012.10:g.101758322G>A
NG_008690.1:g.82189C>T
NG_008690.2:g.122997C>T
ENST00000553106.6:c.1301C>T
ENST00000307000.7:c.1286C>T
ENST00000551114.2:n.963C>T
ENST00000553106.5:c.1301C>T
ENST00000635477.1:c.405C>T
ENST00000635528.1:n.816C>T
NM_000277.2:c.1301C>T
NM_001354304.1:c.1301C>T
NM_000277.3:c.1301C>T
NM_001354304.2:c.1301C>T

Likely Pathogenic

Met criteria codes 4

PP4 PM3_Supporting PM5 PM2

Not Met criteria codes 1

PP3

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1301C>T (p.Ala434Val) variant in PAH has been reported in 1 individual with classic PKU detected with pathogenic variant p.R243X (PMID: 24350308). This variant is absent in population databases. Another missense change at the same amino acid (p.Ala434Asp) is likely

pathogenic by 1 submitter and pathogenic by PAH VCEP. Computational evidence is conflicting. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM5, PM3_supporting, PP4.

Met criteria codes

PP4	✔	A434V seen on 1 allele of a classic PKU patient. BH4 deficiency not assessed/reported. PMID: 24350308
		1286 PKU-patients were genotyped. A434V seen on 1 allele of a classic PKU patient. PubMed:24350308
PM3_Supporting	✔	Found with R243X, parental testing not reported PMID: 24350308
		A434V seen with p.R243* in 1 patient (VarID 588, Pathogenic) PubMed:24350308
PM5	✔	A434D (VarID 102586) is likely pathogenic in ClinVar, and Pathogenic based on ClinGen PAH VCEP
PM2	✔	Absent from ExAC, gnomAD, 1000G, ESP

Not Met criteria codes

PP3	✖	Conflicting predictions of pathogenicity: tolerated/benign in SIFT+Polyphen2, Disease causing in MutationTaster

Curation History

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