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.1139C>T (p.Thr380Met)

CA114369

628 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: 95c70134-5e17-4767-a5b4-84155f4374bd
Approved on: 2018-10-01
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HGVS expressions

NM_000277.1:c.1139C>T
NM_000277.1(PAH):c.1139C>T (p.Thr380Met)
NC_000012.12:g.102843706G>A
CM000674.2:g.102843706G>A
NC_000012.11:g.103237484G>A
CM000674.1:g.103237484G>A
NC_000012.10:g.101761614G>A
NG_008690.1:g.78897C>T
NG_008690.2:g.119705C>T
NM_000277.2:c.1139C>T
NM_001354304.1:c.1139C>T
NM_000277.3:c.1139C>T
ENST00000307000.7:c.1124C>T
ENST00000549247.6:n.898C>T
ENST00000551114.2:n.801C>T
ENST00000553106.5:c.1139C>T
ENST00000635477.1:n.243C>T
ENST00000635528.1:n.654C>T

Pathogenic

Met criteria codes 4

PP4_Moderate PS3 PM3_Very Strong PP3

Not Met criteria codes 2

PM5 PM2

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.1139C>T (p.Thr380Met) variant in PAH has been reported in 1 patient with PAH deficiency (BH4 deficiency excluded). (PP4_Moderate; PMID: 8268925). This variant has 28% enzyme activity (PS3; PMID: 27620137). This variant was detected in trans with multiple known

pathogenic variants: R408W, R261Q, I65T, F299C (PM3_Very-strong; PMID: 7981714). Computational prediction tools and conservation analysis suggest that the c.1139C>T variant may impact the protein (PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PS3, PM3_Very-strong

Met criteria codes

PP4_Moderate	✔	T380M found in 1 patient with PAH deficiency. BH4 deficiency ruled out. Upgraded per ClinGen Metabolism WG. PMID: 8268925 Subjects included 53 unrelated patients presenting with blood phenylalanine levels persistently above 150 umol/l. The criteria for inclusion were: normal serum tyrosine, normal urinary excresion of biopterin and neopterin, and no indication of acquired hyperphenylalaninemia. T380M was found on 1 chromosome. PubMed:8268925
PS3	✔	In vitro residual activity of T380M mutant was 28% of wild type. PMID: 27620137 Transient expression of mutant full-length cDNAs in COS-7 cells yielded PAH proteins with PAH activity levels between 7% and 51% compared to the wild-type enzyme. Higher activity correlated with milder phenotypes (e.g. p.T380M with 28% PAH activity) PubMed:27620137
PM3_Very Strong	✔	Detected in trans with R408W (P), R261Q (P/LP), I65T (P/LP), F299C (P/LP). Upgraded per ClinGen SVI workgroup. PMID: 7981714 In all patients carrying T380M, mutations known to cause classic PKU (R408W, R261Q, I65T, and F299C) were identified on the other chromosome. The mutations identified were confirmed by restriction analysis of PCR products reamplified from genomic DNA in affected subjects and their parents. PubMed:7981714
PP3	✔	Deleterious effect predicted by SIFT, PolyPhen2, MutationTaster

Not Met criteria codes

PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	MAF=0.00463 in gnomAD

Curation History

Showing 1 to 1 of 1 rows

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