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# *Variant: NM_000277.1(PAH):c.1139C>T (p.Thr380Met)*

Version: 1.0

*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
**Published on**: 2019-04-05

## *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

PS3 PP3 PM3_Very Strong PP4_Moderate

**Not Met criteria codes** 2

PM2 PM5

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**

| | | |
|---|---|---|
| **PS3** | ✔ | In vitro residual activity of T380M mutant was 28% of wild type. PMID: 27620137<br><br>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 |
| **PP3** | ✔ | Deleterious effect predicted by SIFT, PolyPhen2, MutationTaster |
| **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<br><br>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 |
| **PP4_Moderate** | ✔ | T380M found in 1 patient with PAH deficiency. BH4 deficiency ruled out. Upgraded per ClinGen Metabolism WG. PMID: 8268925<br><br>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 |

**Not Met criteria codes**

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

Curation History

Showing 1 to 1 of 1 rows