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# *Variant: NM_000277.3(PAH):c.1144T>C (p.Phe382Leu)*

Version: 1.0

*CA386493225*

*556882 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 764ebb0c-185b-4e39-9493-964818951434
**Approved on**: 2021/2/13
**Published on**: 2023/1/28

## *HGVS expressions*

**NM_000277.3:c.1144T>C**
**NM_000277.3(PAH):c.1144T>C (p.Phe382Leu)**
NC_000012.12:g.102843701A>G
CM000674.2:g.102843701A>G
NC_000012.11:g.103237479A>G
CM000674.1:g.103237479A>G
NC_000012.10:g.101761609A>G
NG_008690.1:g.78902T>C
NG_008690.2:g.119710T>C
ENST00000553106.6:c.1144T>C
ENST00000307000.7:c.1129T>C
ENST00000549247.6:n.903T>C
ENST00000551114.2:n.806T>C
ENST00000553106.5:c.1144T>C
ENST00000635477.1:c.248T>C
ENST00000635528.1:n.659T>C
NM_000277.1:c.1144T>C
NM_000277.2:c.1144T>C
NM_001354304.1:c.1144T>C
NM_001354304.2:c.1144T>C

**Pathogenic**

**Met criteria codes** 5

PP4_Moderate PM3 PM2 PS3 PP3

**Not Met criteria codes** 2

PM5 PS1

Evidence Links 1

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.1144T>C (p.Phe382Leu) variant in PAH has been reported in 1 homozygous individual with mild HPA and BH4 deficiency excluded (PP4_Moderate; 0.5 points; PMID: 21147011) and has also been reported in a patient from southern Italy (PMID: 17096675; PMID: 18346471) with mild hyperphenylalanemia (serum Phe 182 umol/L; not specified if BH4 deficiency excluded), who harbored it in presumed trans with the p.R252W variant (Pathogenic in ClinVar by 10 submitters, variation ID 584) (0.5 points) (PM3, 1 point total). This variant was absent in population databases (PM2). Expressed in COS-1 cells, this variant has 18% enzyme activity (PS3; PMID: 22698810). Computational prediction tools suggest that the variant may impact the protein (REVEL = 0.89; PP3). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PS3, PM2, PM3, PP4_moderate, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP4_Moderate** | ✔ | At least one mild HPA patient has been reported (PMID: 21147011) mild HPA (Phe between 120 and 600 µM). BH4 deficiency was excluded by sequencing of PTS and QDPR. |
| **PM3** | ✔ | One c.1146T>C homozygote has been described with mild HPA (PMID: 21147011). In addition, the variant has also been reported in a patient from southern Italy (PMID: 17096675; PMID: 18346471) with mild hyperphenylalanemia (serum Phe 182 umol/L; not specified if BH4 deficiency excluded), who harbored it in presumed trans with the p.R252W variant (Pathogenic in ClinVar by 10 submitters, variation ID 584) (0.5 points) |
| **PM2** | ✔ | This variant is absent from all population cohorts in gnomAD, ExAC, 1000 Genomes, and ESP. |
| **PS3** | ✔ | Expression on COS-1 cells found 18% residual activity for this variant compared to WT.<br>The expression of c.1144T>C (p.F382L) mutant protein in COS-1 cells showed reduced activity compared to wild type PAH protein. Residual activity for mutant p.F382L activity was 18%. Additionally, RT-PCR in patient cells and minigene assay in COS-1 cells suggest that this variant causes skipping of exon 11 which causes NMD.<br>PubMed:22698810 |
| **PP3** | ✔ | Predicted damaging in SIFT, PolyPhen2, and Mutation Taster, REVEL = 0.89. |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | The variant c.1144T>A (p.Phe382Ile), reported in PMID: 29499199, occurs at the same amino acid residue but it is not present in ClinVar and its pathogenicity has not been evaluated. |
| **PS1** | ✖ | The likely pathogenic variant c.1146C>G (p.Phe382Leu) with the same amino acid change has been reported in at least one proband. It is not evaluated here to avoid circularity. |

Curation History

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