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# *Variant: NM_000277.3(PAH):c.231T>G (p.Tyr77Ter)*

Version: 1.0

*CA229493*

*102635 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 566c47a8-afb9-4069-998d-80ae462e7113
**Approved on**: 2023/10/15
**Published on**: 2023/10/15

## *HGVS expressions*

**NM_000277.3:c.231T>G**
**NM_000277.3(PAH):c.231T>G (p.Tyr77Ter)**
NC_000012.12:g.102894856A>C
CM000674.2:g.102894856A>C
NC_000012.11:g.103288634A>C
CM000674.1:g.103288634A>C
NC_000012.10:g.101812764A>C
NG_008690.1:g.27747T>G
NG_008690.2:g.68555T>G
ENST00000553106.6:c.231T>G
ENST00000307000.7:c.216T>G
ENST00000546844.1:c.231T>G
ENST00000548677.2:n.318T>G
ENST00000548928.1:n.153T>G
ENST00000549111.5:n.327T>G
ENST00000550978.6:c.215T>G
ENST00000551337.5:c.231T>G
ENST00000551988.5:n.320T>G
ENST00000553106.5:c.231T>G
NM_000277.1:c.231T>G
NM_000277.2:c.231T>G
NM_001354304.1:c.231T>G
NM_001354304.2:c.231T>G

**Pathogenic**

**Met criteria codes** 4

PM2_Supporting PM3 PVS1 PP4_Moderate

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

*Phenylketonuria VCEP*

**The NM_000277.3(PAH):c.231T>G (p.Tyr77Ter) is a nonsense variant in exon 3/13 of PAH, and is predicted to result in PTC with removal of >10% of the protein and NMD (PVS1). The variant is absent from population databases including gnomAD, ExAC, and ESP, and is present at an extremely low allele frequency (MAF < 0.0002) in the 1000 Genomes (PM2_supporting). The variant has been previously reported in a patient with PKU (plasma Phe level not specified) and BH4 deficiency excluded (PMID: 9860305; PMID: 21307867) (PP4_Moderate); the patient's genotype was not specified. It has also been noted (PMID: 28982351) in a patient with mild PKU (plasma Phe 720 uM) and BH4 deficiency excluded (PP4_Moderate), who harbored it in trans with the p.Asp101Asn (Likely Pathogenic in ClinVar, ID 553851) and p.Gly247Arg (Likely Pathogenic in ClinVar, ID 102816) alleles (PM3). In summary, this variant meets criteria to be classified as for PAH. PAH-specific ACMG/AMP criteria applied: PVS1, PM2_supporting, PM3, PP4_Moderate.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2_Supporting** | ✔ | The variant is absent from population databases including gnomAD, ExAC, and ESP, and is present at an extremely low allele frequency (MAF < 0.0002) in the 1000 Genomes (PM2). |
| **PM3** | ✔ | It has also been noted (PMID: 28982351) in a patient with mild PKU (plasma Phe 720 uM) and BH4 deficiency excluded (PP4_Moderate), who harbored it in trans with the p.Asp101Asn (Likely Pathogenic in ClinVar, ID 553851) and p.Gly247Arg (Likely Pathogenic in ClinVar, ID 102816) alleles (PM3). |
| **PVS1** | ✔ | The NM_000277.3(PAH):c.231T>G (p.Tyr77Ter) is a nonsense variant in exon 3/13 of PAH, and is predicted to result in PTC with removal of >10% of the protein and NMD (PVS1). |
| **PP4_Moderate** | ✔ | The variant has been noted (PMID: 28982351) in a patient with mild PKU (plasma Phe 720 uM) and BH4 deficiency excluded (PP4_Moderate). |

Curation History

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