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# *Variant: NM_000277.1:c.935G>T*

Version: 1.0

*CA16020902*

*1458264 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** de8f7a81-6f3d-41f8-b294-95df94840919
**Approved on**: 2023/12/30
**Published on**: 2023/12/30

## *HGVS expressions*

**NM_000277.1:c.935G>T**
NC_000012.12:g.102846929C>A
CM000674.2:g.102846929C>A
NC_000012.11:g.103240707C>A
CM000674.1:g.103240707C>A
NC_000012.10:g.101764837C>A
NG_008690.1:g.75674G>T
NG_008690.2:g.116482G>T
ENST00000553106.6:c.935G>T
ENST00000307000.7:c.920G>T
ENST00000549247.6:n.694G>T
ENST00000551114.2:n.597G>T
ENST00000553106.5:c.935G>T
ENST00000635477.1:c.74-2498G>T
ENST00000635528.1:n.450G>T
NM_000277.2:c.935G>T
NM_001354304.1:c.935G>T
NM_000277.3:c.935G>T
NM_001354304.2:c.935G>T

**Pathogenic**

**Met criteria codes** 5

PM3_Very Strong | PS3_Supporting | PM2_Supporting | PP3 | 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:c.935G>T (p.Gly312Val) is a missense variant in exon 9/13 of PAH. The variant was found to reduce PAH enzymatic activity to 6-7% of wild-type enzyme activity in transfected cells (PMID: 18590700) (PS3_supporting). The variant has been noted in at**

**least six PKU patients with BH4 deficiency excluded (PP4_Moderate), five of whom harbored it in confirmed trans with a Pathogenic or Likely Pathogenic variant (5 points; PM3_VeryStrong). The variant has been reported as a single heterozygous variant in a Chinese patient with mild PKU; BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes and by sequencing of genes in the BH4 cofactor metabolism pathway (PMID: 14722928). It has also been found in confirmed trans with c.913-7A>G (Likely Pathogenic per ClinGen PAH VCEP) in a Chinese patient with classic PKU (plasma Phe ≥ 1200 µmol/L); BH4 deficiency was said to be ruled out (PMID: 24401910). It was found in four Chinese PKU patients (BH4 deficiency excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes and by sequencing of genes in the BH4 cofactor metabolism pathway) in the following cases: two patients with mild hyperphenylalanemia in confirmed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP); one patient with classic PKU in confirmed trans with the p.R413P variant (Pathogenic per ClinGen PAH VCEP); and one patient with mild hyperphenylalanemia in confirmed trans with the p.T372S variant (Likely Pathogenic per ClinGen PAH VCEP) (PMID: 30050108). One heterozygote for the variant is present in gnomAD, corresponding to a global frequency of 0.00000398 and a maximum population frequency of 0.0000544 (East Asian), under the frequency cutoff of 0.0002 for use of PM2 (PM2_supporting). The variant is predicted damaging by multiple in-silico missense predictors, including REVEL (REVEL score 0.942) (PP3). Classification: Pathogenic Supporting Criteria: PM3_VeryStrong; PS3_supporting; PM2_supporting; PP4_Moderate; PP3**

**Met criteria codes**

| | | |
|---|---|---|
| **PM3_Very Strong** | ✔ | The variant has been noted in five patients in confirmed trans with a Pathogenic or Likely Pathogenic variant (5 points; PM3_VeryStrong): c.913-7A>G (Likely Pathogenic per ClinGen PAH VCEP) in a Chinese patient with classic PKU (PMID: 24401910); two patients with mild hyperphenylalanemia in confirmed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP); one patient with classic PKU in confirmed trans with the p.R413P variant (Pathogenic per ClinGen PAH VCEP); and one patient with mild hyperphenylalanemia in confirmed trans with the p.T372S variant (Likely Pathogenic per ClinGen PAH VCEP) (PMID: 30050108). |
| **PS3_Supporting** | ✔ | 7% residual enzyme activity (PMID: 18590700) |
| **PM2_Supporting** | ✔ | One heterozygote for the variant is present in gnomAD, corresponding to a global frequency of 0.00000398 and a maximum population frequency of 0.0000544 (East Asian), under the frequency cutoff of 0.0002 for use of PM2. |
| **PP3** | ✔ | All major computational evidence suggest damaging effect (REVEL=0.942) |
| **PP4_Moderate** | ✔ | The variant has been noted in at least six PKU patients with BH4 deficiency excluded (PP4_Moderate), five of whom harbored it in confirmed trans with a Pathogenic or Likely Pathogenic variant (5 points; PM3_VeryStrong). The variant has been reported as a single heterozygous variant in a Chinese patient with mild PKU; BH4 deficiency was excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes and by sequencing of genes in the BH4 cofactor metabolism pathway (PMID: 14722928). It has also been found in confirmed trans with c.913-7A>G (Likely Pathogenic per ClinGen PAH VCEP) in a Chinese patient with classic PKU (plasma Phe ≥ 1200 µmol/L); BH4 deficiency was said to be ruled out (PMID: 24401910). It was found in four Chinese PKU patients (BH4 deficiency excluded by analysis of urinary pterins and dihydropteridine reductase activity in erythrocytes and by sequencing of genes in the BH4 cofactor metabolism pathway) in the following cases: two patients with mild hyperphenylalanemia in confirmed trans with the p.R241C variant (Pathogenic per ClinGen PAH VCEP); one patient with classic PKU in confirmed trans with the p.R413P variant (Pathogenic per ClinGen PAH VCEP); and one patient with mild hyperphenylalanemia in confirmed trans with the p.T372S variant (Likely Pathogenic per ClinGen PAH VCEP) (PMID: 30050108). |

Curation History

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