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# *Variant: NM_000277.3(PAH):c.117C>G (p.Phe39Leu)*

Version: 1.0

*CA251537*

*605 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 3e20a694-2d0a-4342-b7b4-eeea90dbee7d
**Approved on**: 2020/3/27
**Published on**: 2021/6/9

## *HGVS expressions*

**NM_000277.3:c.117C>G**
**NM_000277.3(PAH):c.117C>G (p.Phe39Leu)**
NC_000012.12:g.102912842G>C
CM000674.2:g.102912842G>C
NC_000012.11:g.103306620G>C
CM000674.1:g.103306620G>C
NC_000012.10:g.101830750G>C
NG_008690.1:g.9761C>G
NG_008690.2:g.50569C>G
ENST00000553106.6:c.117C>G
ENST00000307000.7:c.102C>G
ENST00000546844.1:c.117C>G
ENST00000548677.2:n.204C>G
ENST00000548928.1:n.39C>G
ENST00000549111.5:n.213C>G
ENST00000550978.6:c.101C>G
ENST00000551337.5:c.117C>G
ENST00000551988.5:n.206C>G
ENST00000553106.5:c.117C>G
ENST00000635500.1:n.85C>G
NM_000277.1:c.117C>G
NM_000277.2:c.117C>G
NM_001354304.1:c.117C>G
NM_001354304.2:c.117C>G

**Pathogenic**

**Met criteria codes** 4

PP1 PP4 PM2 PM3_Very Strong

**Not Met criteria codes** 1

PS3

Evidence Links 0

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.117C>G (p.Phe39Leu) variant in PAH has been reported in multiple individuals with PKU. (PMID: 23430918, 8659548, 8406445, 2063869). This variant has an extremely low allele frequency in ExAC, gnomAD, 1000 Genomes, ESP (MAF=0.00016). This variant was detected with multiple pathogenic variants: T81P, V177L (PMID: 8659548), F55fsdelT (2 patients, PMID: 15557004), p.I65T, p.R408W (4 patients), p.R252W, p.E280K, c.1066-11G>A, c.1315+1G>A (PMID: 23430918). There is cosegregation with disease in affected siblings in 2 families PMID: 2063869, 8592329). In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4, PP1.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✔ | Cosegregation with disease in 2 siblings in each of 2 families PMID: 2063869, PMID: 8592329 |
| **PP4** | ✔ | Detected in multiple affected individuals: PMID: 23430918, PMID: 8659548, PMID: 8406445, PMID: 2063869 |
| **PM2** | ✔ | Extremely low frequency if recessive in ExAC, gnomAD, 1000 Genomes, ESP (MAF=0.00016) |
| **PM3_Very Strong** | ✔ | detected in trans with p.Ser349Arg PMID: 2063869 (P, OMIM). Detected with T81P (P, 1 submitter), V177L (P-3/LP-1) PMID: 8659548 R48W, F55fsdelT (2 patients, P-5) PMID: 15557004 p.I65T (P-10); p.R408W (4 patients, P-14); p.R252W (P-7); p.E280K (P-9); c.1066-11G>A (P-7); c.1315+1G>A (P-13) PMID: 23430918 parental analysis not reported |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PS3** | ✖ | p.F39L had PAH activity of: 73% (COS cells); 67% (e. coli); 47% (TNT-T7); and 46% (HEK293) |

Curation History

Showing 1 to 1 of 1 rows

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