

*Variant: NM\_000277.1(PAH):c.1238G>C (p.Arg413Pro)*

CA229414 [↗](#)

592 (ClinVar) [↗](#)

**Gene:** PAH ([HGNC:5053](#))

**Condition:** phenylketonuria ([MONDO:0009861](#))

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** ce8fbaf1-f9e2-43cc-ac9c-6b77a1fd68a0

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**Published on:** 2018-12-10

### *HGVS expressions*

**NM\_000277.1(PAH):c.1238G>C (p.Arg413Pro)**

**NM\_000277.1:c.1238G>C**

NC\_000012.12:g.102840477C>G

CM000674.2:g.102840477C>G

NC\_000012.11:g.103234255C>G

CM000674.1:g.103234255C>G

NC\_000012.10:g.101758385C>G

NG\_008690.1:g.82126G>C

NG\_008690.2:g.122934G>C

NM\_000277.2:c.1238G>C

NM\_001354304.1:c.1238G>C

NM\_000277.3:c.1238G>C

ENST00000307000.7:c.1223G>C

ENST00000551114.2:n.900G>C

ENST00000553106.5:c.1238G>C

ENST00000635477.1:n.342G>C

ENST00000635528.1:n.753G>C

**Pathogenic**

Met criteria codes **5**

PS3

PP4\_Moderate

PP3

PM2

PM3

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

#### ***Phenylketonuria VCEP***

**PAH-specific ACMG/AMP criteria applied:** PS3: In vitro expression of altered protein in COS cells produces severe decrease of PAH activity (<3%); PM2: Extremely low frequency. ExAC MAF=0.00012; PP4\_Moderate: Detected in PKU patients, BH4 deficiency excluded; PP3: Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.895; PM3: Detected with V388M (pathogenic) in 2 patients (PMID:9860305; PMID:21307867). In summary this variant meets criteria to be classified as pathogenic for phenylketonuria in an autosomal recessive manner based on the ACMG/AMP criteria applied as specified by the PAH Expert Panel: (PS3, PM2, PP4\_Moderate, PP3, PM3).

Met criteria codes

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                   |   |                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---|----------------------------------------------------------------------------------------------------|
| PS3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   | ✓ | In vitro expression of altered protein in COS cells produces severe decrease of PAH activity (<3%) |
| PP4_Moderate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  | ✓ | Detected in PKU patients, BH4 deficiency excluded                                                  |
| PP3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  | ✓ | Predicted deleterious in SIFT, Polyphen-2, MutationTaster. REVEL=0.895                             |
| PM2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                   | ✓ | Extremely low frequency. ExAC MAF=0.00012                                                          |
| PM3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  | ✓ | Detected with V388M (pathogenic) in 2 patients                                                     |
| <div>A132V (not in ClinVar) /R413P. Two patients with compound heterozygote mutations of V388M (VarID619, Pathogenic) /R413P. <a href="#">PubMed:21307867</a> </div> <div>We confirmed that 7 patients were homozygous for R413P by using direct sequencing and demonstrated that the parents were heterozygous carriers for the same mutations as the patients. <a href="#">PubMed:9860305</a> </div> |                                                                                   |   |                                                                                                    |

Curation History 



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