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# *Variant: NM_000277.1(PAH):c.1289T>C (p.Leu430Pro)*

Version: 1.0

*CA229426*

*102585 (ClinVar)*

**Gene**: PAH (HGNC:5053)
**Condition**: phenylketonuria (MONDO:0009861)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 4f473c18-c77e-4640-a9b2-3cfa3f248926
**Approved on**: 2020/8/17
**Published on**: 2021/12/12

## *HGVS expressions*

**NM_000277.1(PAH):c.1289T>C (p.Leu430Pro)**
**NM_000277.1:c.1289T>C**
NC_000012.12:g.102840426A>G
CM000674.2:g.102840426A>G
NC_000012.11:g.103234204A>G
CM000674.1:g.103234204A>G
NC_000012.10:g.101758334A>G
NG_008690.1:g.82177T>C
NG_008690.2:g.122985T>C
ENST00000553106.6:c.1289T>C
ENST00000307000.7:c.1274T>C
ENST00000551114.2:n.951T>C
ENST00000553106.5:c.1289T>C
ENST00000635477.1:c.393T>C
ENST00000635528.1:n.804T>C
NM_000277.2:c.1289T>C
NM_001354304.1:c.1289T>C
NM_000277.3:c.1289T>C
NM_001354304.2:c.1289T>C

**Likely Pathogenic**

**Met criteria codes** 4

PM2 PP4_Moderate PP3 PM3_Strong

**Not Met criteria codes** 2

PM5 PS3

Evidence Links 3

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Phenylketonuria VCEP***

**The c.1289T>C (p.Leu430Pro) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded, PMID: 21307867). This variant is absent in population databases. This variant was detected with pathogenic variants: p.R241C (PMID: 21147011); p.S70del, p.R241C (PMID: 30050108); c.728G>A, p.R243Q (PMID: 31355225). Computational evidence support a deleterious effect. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PP4_Moderate, PM2, PM3_strong, PP3.**

**Met criteria codes**

| | | |
|---|---|---|
| **PM2** | ✔ | Absent from ExAC, gnomAD, 1000G, ESP |
| **PP4_Moderate** | ✔ | L430P was found in 1 patient with PAH deficiency. BH4 deficiency excluded by analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine. PMID: 21307867<br><br>This study enrolled 203 Japanese residents with a serum phenylalanine level higher than 0.18 mm. PAH deficiency was diagnosed on the basis of absence of neurologic deterioration on a low phenylalanine diet, analysis of dihydropteridine reductase activity in red blood cells, biopterin loading test and/or pteridine analysis in urine. L430P was found on 1 allele. PubMed:21307867 |
| **PP3** | ✔ | Predicted deleterious in SIFT, PolyPhen2, MutationTaster, REVEL=0.976 |
| **PM3_Strong** | ✔ | L430P found with pathogenic variants (R241C, A300S). parental analysis not performed PMID: 21147011; p.L430P/p.Y414* (not in ClinVar); p.L430P/p.S70del (P 3 submitters); p.R241C/p.L430P. Validation tests on parents performed. PMID: 30050108; p.Ile324Asn, (not in ClinVar) variable sites in patient genes were aligned with the corresponding sites from the respective parents. PMID: 29316886; c.728G > A, p.R243Q (P 11 submitters). Parents were also investigated to confirm their carrier status. PMID: 31355225 3.5 pts<br><br>L430P found in trans with A300S (VarID 92751, Pathogenic in ClinVar) in 1 PKU patient, and R241C (VarID 102803, Pathogenic in ClinVar) in 1 PKU patient. PubMed:21147011 |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM5** | ✖ | Only variant found in this codon in ClinVar |
| **PS3** | ✖ | Using the phenylalanine breath test, cumulative recovery rate (CRR) for a classical PKU patient (R413P/L430P) is close to 0 vs. ~10-15 for carriers or controls.<br><br>We performed the phenylalanine breath test as reliable method to determine BH4 responsiveness. Phenylalanine breath test quantitatively measures the conversion of L-[1-13C] phenylalanine to 13CO2. 20 Japanese patients with HPA were examined with a dose of 10 mg/kg of 13C-phenylalanine with or without a dose of 10 mg . kg(-1) . d(-1) of BH4 for 3 d. Figure 3 shows the phenylalanine breath test [cumulative recovery rate (CRR)] for a classical PKU patient (R413P/L430P) is close to 0 vs. ~10-15 for carriers or controls. PubMed:15319459 |

Curation History

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