

Variant: *NM_000277.1(PAH):c.631C>A (p.Pro211Thr)*

Version: 1.0

CA229666 [↗](#)

102766 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: f456bf29-4223-48fc-b2ed-ac0b0bc873a3

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HGVS expressions

NM_000277.1:c.631C>A

NM_000277.1(PAH):c.631C>A (p.Pro211Thr)

NC_000012.12:g.102855211G>T

CM000674.2:g.102855211G>T

NC_000012.11:g.103248989G>T

CM000674.1:g.103248989G>T

NC_000012.10:g.101773119G>T

NG_008690.1:g.67392C>A

NG_008690.2:g.108200C>A

ENST00000553106.6:c.631C>A

ENST00000307000.7:c.616C>A

ENST00000549111.5:n.727C>A

ENST00000553106.5:c.631C>A

NM_000277.2:c.631C>A

NM_001354304.1:c.631C>A

NM_000277.3:c.631C>A

NM_001354304.2:c.631C>A

Pathogenic

Met criteria codes **4**

PP4_Moderate

PM3_Very Strong

PP3

PM2

Not Met criteria codes **2**

PS3

PM5

Evidence Links **2**

Expert Panel

Phenylketonuria VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.631C>A (p.Pro211Thr) variant in PAH has been reported in multiple individuals with PAH deficiency (BH4 deficiency excluded) (PMID: 11708866, 21147011, 1619813). This variant has an extremely low allele frequency (MAF=0.00004) in gnomAD. It was detected with multiple pathogenic variants: IVS10-11G>A (4 patients, PMID: 21147011); p.R261Q in 2 unrelated patients (PMID: 11708866); p.R408W

(PMID: 9429153); p.G272X (PMID: 16198137). Computational prediction tools and conservation analysis support a deleterious effect on the protein. In summary, this variant meets criteria to be classified as pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM3_very-strong, PM2, PP4_Moderate, PP3.

Met criteria codes

PP4_Moderate			<p>P211T seen in 8 patients with PKU. BH4 deficiency excluded in 6 patients. (PMID: 11708866, PMID: 21147011; PMID: 1619813)</p> <p>588 hyperphenylalaninemic patients were investigated. Assessment included PAH gene and genes of the BH4 synthesis/recycling pathways (PTS and QDPR). p.P211T was seen with IVS10-11G>A in 4 patients. PubMed:21147011</p> <p>Discordant metabolic phenotypes (mild PKU and MHP) were observed in two unrelated patients bearing the same R261Q/P211T genotype. PubMed:11708866</p>
PM3_Very Strong			<p>P211T found with IVS10-11G>A in 4 patients, parental analysis not reported PMID: 21147011; and R261Q in 2 unrelated patients, parental analysis not reported. PMID: 11708866, both Pathogenic; R408W (P), parental analysis not reported PMID: 9429153; G272X (P) parental analysis not reported PMID: 16198137. 4.0 pts</p> <p>p.P211T was seen with IVS10-11G>A (VarID 607, Pathogenic) in 4 patients. PubMed:21147011</p> <p>R261Q/P211T (VarID582, Pathogenic/Likely Pathogenic) PubMed:11708866</p>
PP3			<p>Damaging in SIFT, Polyphen, Mutation Taster</p>
PM2			<p>Not found in ExAC, 1000G, ESP. MAF=0.00004 in gnomAD</p>

Not Met criteria codes

PS3			<p>Analyzed in vitro by the pCDNA3/COS-7 eukaryotic expression system and found an activity of 72% compared to normal PAH.</p> <p>Analyzed three missense mutations L41F, T92I, and P211T in vitro by the pCDNA3/COS-7 eukaryotic expression system and found an activity of 10, 76, and 72%, respectively, compared to normal PAH. PubMed:11708866</p>
PM5			<p>p.Pro211Leu (VarID 120283) Likely Pathogenic in ClinVar 3 submitters</p>

Curation History 

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