MNK Publication

International Journal of Latest Research in Science and Technology **ISSN (Online):2278-5299**
Volume 7, Issue 6: Page No.12 - 17 , November - December 2018
https://www.mnkpublication.com/journal/ijlrst/index.php

HAPLOTYPE ANALYSIS OF SINGLE NUCLEOTIDE POLYMORPHISMS OF CYP1A1 AND CYP1A2 AND ITS RELATIONSHIP WITH THE DEVELOPMENT OF PORPHYRIA CUTANEA TARDA.

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Running Head: CYPs SNPs and Porphyria Cutanea Tarda

***Abstract* : *Objective*: Porphyria Cutanea Tarda results from decrease hepatic uroporphyrinogen decarboxylase activity. There are two principal types: sporadic or acquired and familial or hereditary Porphyria Cutanea Tarda. Hereditary Porphyria Cutanea Tarda is observed in 25-30% of the patients in whom one allele of the uroporphyrinogen decarboxylase gene reduces the enzyme activity by approximately 50% in all tissues. There are experimental evidences that suggest a possible relationship between CYP1A1, CYP1A2 and Porphyria Cutanea Tarda symptomatology development but the results described in different populations are very conflictive.The aim of this work is provide additional evidences about the participation of the CYP system on the manifestation of this disease.**

Subjets/Methods: We analyse the polymorphisms already described in these CYPs isoforms in 112 Porphyria Cutanea Tarda Argentinian patients and 89 controls. Of these 64 were used for haplotype analysis. The polymorphisms were detected by RFLP-PCR or sequencing.

Results: For CYP1A2*1F polymorphism C allele (wt) was exceptionally the less frequent while the polymorphic A allele, with an increased transcriptional activity, resulted to be the risk allele.

For CYP1A1 m4 polymorphism, for which are not previous reports about this effect, our results indicated that the A variant would be a risk factor to develop the disease.

For m2 polymorphism we obtained contradictory results depending on the groups compared.

The risk haplotype calculated with the snpSTATs was m4-m2-m1-1A2: C-G-C-C.

Conclusions: These results indicated that, among other factors, these polymorphisms would be related with Porphyria Cutanea Tarda development.

I. INTRODUCTION

The porphyrias are a group of metabolic diseases which results from the partially deficiency of one of the enzymes of the heme biosynthetic pathway (Fig. 1).

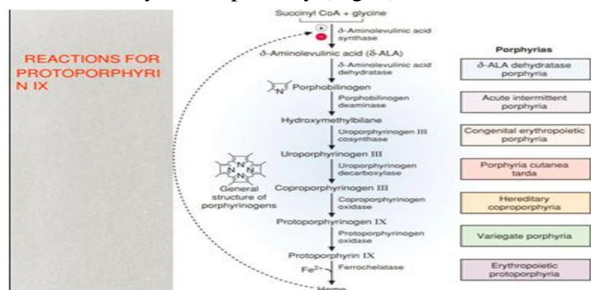

Figure 1. Pathway of heme biosynthesis. Heme biosynthesis begins in the mitochondria from glycine and succinyl-CoA, continues in the cytosol, and ultimately is completed within the mitochondria. PBG: porphobilinogen, ALA: δ-aminolevulinic acid. URL: https://www.google.com.ar/heme biosynthesis.

Porphyria Cutanea Tarda (PCT; OMIM 176100), the most common type of porphyria, is due to a decreased activity of uroporphyrinogen decarboxylase (UROD; E.C.4.1.1.37). This cytosolic enzyme catalyzes the fifth step in the heme biosynthetic pathway (Fig. 1), the sequential decarboxylation of the four acetate side chains of uroporphyrinogen to form coproporphyrinogen [1,2]. PCT usually develops in adulthood and is characterized by hepatic accumulation of uroporphyrinogen and other highly carboxylated porphyrinogens that circulate in plasma and are excreted in

Publication History

Manuscript Received	:	**21 December 2018**
Manuscript Accepted	:	**3 January 2019**
Revision Received	:	**24 January 2019**
Manuscript Published	:	**29 January 2019**

urine as porphyrins [2,3]. The overproduction of porphyrins is the reason for the major clinical manifestations of the disease, cutaneous photosensitivity with blistering on areas exposed to sun, skin fragility, hyperpigmentation and hypertrichosis [2]. Three clinically similar forms of PCT can be distinguished: A-PCT (acquired PCT), H-PCT (hereditary PCT) and type III PCT [2,4,5]. H-PCT is an autosomal dominant disorder with low penetrance in which the UROD activity is reduced to about 50% in all tissues due to mutations in heterozygosis in the UROD gene. H-PCT represents about 25-30% of PCT patients. Most PCT patients are A-PCT, without mutations in the UROD gene and the deficiency in enzymatic activity is restricted to the liver [2,4,5]. Type III PCT is a rare form similar to A-PCT but, while the A-PCT does not show a familial pattern, type III PCT is associated with a familial history for the disease [5]. The clinical manifestation of PCT is frequently associated with exposure to precipitating factors including iron overload, alcohol abuse, use of estrogens, hepatitis C virus infection and other hepatothropic virus, nitrosamines from tobacco smoke, etc. [2,3,6–8]. Hereditary hemochromatosis associated with the HFE gene is the most common genetic cause of iron overload and inheritance of HFE mutations is prevalent in PCT patients in some countries [7]. Otherwise, mutations in HFE gene do not play a relevant role in the triggering of PCT in Argentina [9].

The clinical expression of the disease is a consequence of a marked deficiency in the UROD activity in the liver caused by a competitive inhibitor (uroporphomethene) generated in an iron-dependent oxidation of uroporhyrinogen [10].

There are experimental evidences that suggest a possible relationship between CYP1A1, CYP1A2 and PCT symptomatology development. In a murine model it was demonstrated that the porphyrinogenic agent hexaclorobencene (HCB) induced hepatic accumulation of URO, due to the formation of metabolites, products of the biotransformation of HCB by those isoforms, inhibiting the hepatic URO-D [11]. Moreover employing murine models of PCT it was observed that UROD activity was inhibited by a product of the oxidation of Urogen (uroporphometene) by the CYP1A2 [10].

So, considering that some of the drugs not recommended for use in porphyric patients are metabolized by these CYPs, the presence of polymorphisms in these molecules would influence the Porphyria triggering.

CYP1A1 is involved in the metabolization of estrogens and carcinogens to their inactive derivatives but occasionally converts the chemicals to more potent carcinogens. SNPs are reported in CYP1A1 and has been described that the frequencies are highly variable between ethnicities and populations. The CYP1A1*2A, rs4646903 (m1 polymorphism) is a T to C transition at 6235 position located in the 3' non-coding region creating a MspI restriction site. The CYP1A1*2C, rs1048943, (m2 polymorphism) is an A to G transition giving rise to a HincII restriction site at position 4889 in exon 7 changing the isoleucine to valine at codon 462 in heme binding region. The m3 polymorphism is a T to C transition at position 5639 which creates a MspI restriction site in 3' non-coding region only found in African American population. The CYP1A1*4, rs.1799814 (m4 polymorphism) which have not been extensively studied, is a C to A transversion at position 4887 leading the threonine to asparagine substitution at codon 461 which leads to the loss of a BsaI restriction site [12,13].

The CYP1A2 gene cluster has been mapped on chromosome 15q24.1, with close link between CYP1A1 and CYP1A2 sharing a common 5'-flanking region. CYP1A2 is located approximately 25 kb away from CYP1A1 on chromosome 15. Human CYP1A2 is one of the main CYPs in human liver and metabolizes a number of several clinical drugs (clozapine, tacrine, tizanidine, and theophylline; some procarcinogens (benzo[α]pyrene and aromatic amines) and several important endogenous compounds (steroids). CYP1A2 is subject to reversible and/or irreversible inhibition by a number of drugs, natural substances and other compounds. A large interindividual variability in the expression and activity of CYP1A2 has been observed, which is largely caused by genetic, epigenetic and environmental factors.

To date, more than 15 variant alleles and series of subvariants of the CYP1A2 gene have been identified and some of them have been associated with altered drug clearance and disease susceptibility. One of the most studied is the promoter variant C/A in the intron region at nucleotide -163 bp. Although C allele is consider the wt, A allele is the most frequent in the population and increases the amount of the enzyme and so its catalytic capacity, C give rise to a restriction site for ApaI.

Epidemiological studies have shown inconsistent results about CYP1A1 and CYP1A2 polymorphisms and porphyria development among various populations ([14], [15], [16], [17]) so we decided to investigate the presence or not of these polymorphisms in our population and if they are related to PCT development.

II. MATERIALS/SUBJETS and METHODS

1. Subjects

A total of 112 samples: 36 H-PCT, 76 A-PCT and 89 controls, carefully selectionated for not being consumers of porphyrinogenic drugs through an oral questionare were included in the study. We calculated genotype and allele frequencies; risk genotype and allele were estimated with the vccSTATs. Of these 112 samples, 64: 24 controls, 23 F-PCT, 17 A-PCT were used to estimate the risk haplotype with snpSTATs.

Mean age at PCT diagnosis was 47,5 years (23–77 years) and the average age of appearance of the first manifestations was 42 years (range from 27 to 61 years).

2. Methods

Biochemical studies included plasma porphyrins index (PPI) and total urinary porphyrins (UTP) with its corresponding chromatography in thin layer showing a preponderance of highly carboxylated porphyrins [18].

UROD activity was about 50% diminished in cases of H-PCT which were also genetically diagnosted [19].

Genomic DNA was extracted from EDTA whole blood samples using Illustra blood genomic Prep Mini spin Kit (Bioneer). Target DNA was amplified with the corresponding pair of primers (Sigma-Aldrich) depending on the fragment to be amplified in each CYP (Table1) and then treated with the corresponding restriction enzymes: ApaI, BsaI and HincII (New England Biolabs) and also by sequencing (Macrogen) when the pattern obtained in the agarose gel was not sufficiently clear.

CYP1A1
m2m4 F: 5' GAACTGCCACTTCAGCTGTCT 3' m2m4 R: 5' GAAAGACCTCCCAGCGGTCA 3'

CYP1A2
1A2 F: 5' GGAAGGTATCAGCAGAAAGCC 3' 1A2 R: 5' GGCTCATCCTTGACAGTGCC 3'

Table 1. PCR primers for the study of polymorphisms of CYPs1A1 (m2-m4) and CYP1A2.

3. Statistical Analysis

The genotype and allele frequencies were estimated for each group and polymorphism. The statistic was done with snpSTATS.

With vccSTATs we contrasted each PCT group with controls (in a contingence table 2x2) to estimate risk genotype or allele with the parameters: odds ratio (OD), p Fisher<0.05 and 95 % confidential interval (CI).

The mutant genotype or allele was contrasted with the wt to estimate the risk allele and genotype.

The risk haplotype was calculated using the snpSTATS program contrasting each group of PCT with controls supposing that our population meet the Hardy-Weinberg law.

4. Databases

The Human Database https://www.ncbi.nlm.nih.gov/ was used for information about reported polymorphisms in these genes.

5. Ethical approval and consent to participate

Informed consent was obtained from all patients following the standards of UNESCO Declarations-DD.HH. Genome and Genetic Data (www.unesco.org/shs/ethics), Declaration of Helsinki was followed and the study was approved by the Institutional Research Ethics Committee of the Research Center on Porphyrins and Porphyrias (CIPYP) - National Scientific and Technical Research Council (CONICET), University of Buenos Aires (UBA).

III. RESULTS

The following Figures show the allele and genotype frequencies calculated for the different polymorphisms in subgroups stratified by familial, acquired and total PCT patients and controls.

In all cases the genotype or allele more frequent is put first except for CYP1A2*1F.

Polymorphism CYP1A2*1F (-163 C/A):
Figures 2 and 3 show the genotype and allele frequencies for this polymorphism respectively.

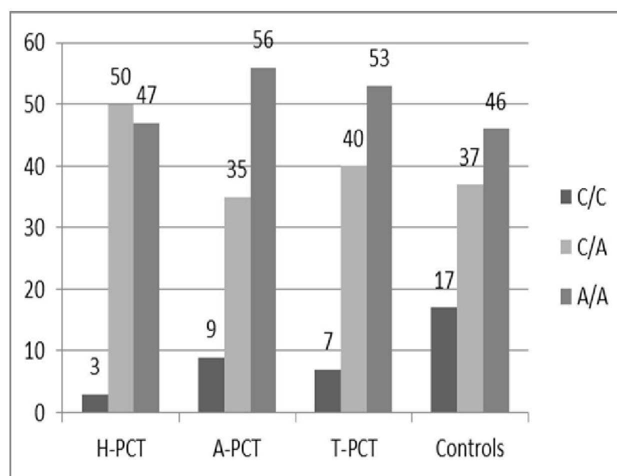

Figure 2. Genotype frequencies for CYP1A2*1F (C/A)

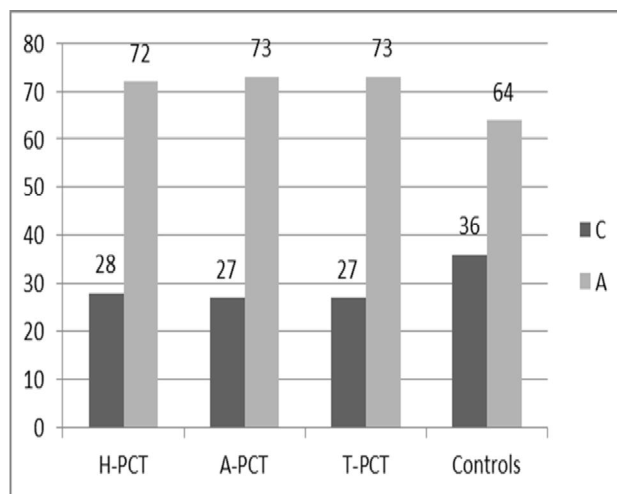

Figure 3. Allele frequencies for CYP1A2*1F (C/A)

Applying vccSTATs program significant results are present in Table 2.

H-PCT vs Controls A/C vs C/C	T-PCT vs Controles A/A vs C/C
OR=8.58 1.04<IC<70.61	OR=2.81 1.08<IC<7.33
pf=0.018	pf=0.027
Risk genotype	Risk genotype

Table 2. Statistic with genotype frequencies

CYP1A1:
Polymorphism CYP 1A1*4 (m4):

Figures 4 and 5 show the genotype and allele frequencies for this polymorphism respectively.

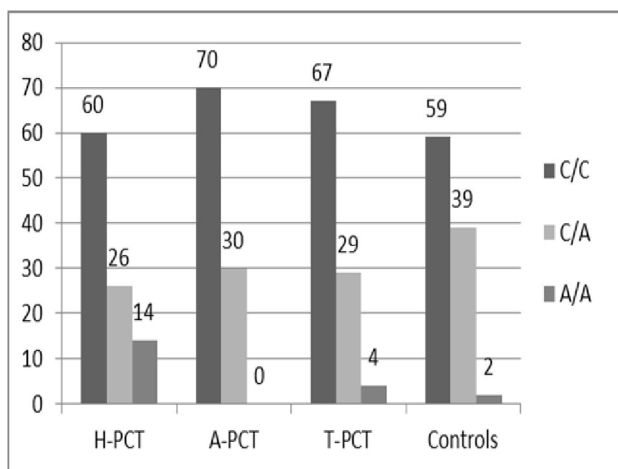

Figure 4. Genotype frequencies of m4 polymorphism (C/A)

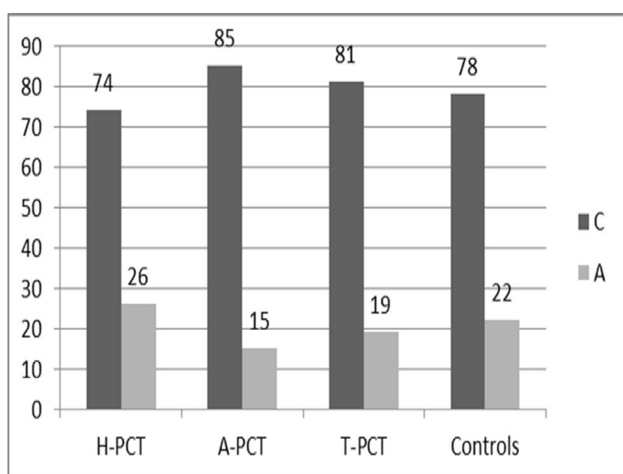

Figure 5. Allele frequencies of m4 polymorphism (C/A)

Applying vccSTATs program significant results are present in Table 3.

H-PCT vs Controls A/A vs C/C	H-PCT vs Controls A/A vs C/A	H-PCT vs A-PCT A/A vs C/C	H-PCT vs A-PCT A/A vs C/A
OR= 5.76 1.04<CI<31.89	OR=8.75 1.47<CI<52.1	OR= 22.17 1.16<CI<423	OR= 22 1.09<CI<442
pf=0.040	pf= 0.016	pf= 0.0056	pf= 0.0087
Risk genotype		Risk genotype	

H-PCT vs A-PCT
OR= 2.01 1.02<CI<3.98
pf=0.0034
Risk allele

Table 3. Statistic with genotype and allele frequencies.

<u>Polymorphism CYP 1A1*2C (m2)</u>:
Figures 6 and 7 show the genotype and allele frequencies for the polymorphism respectively.

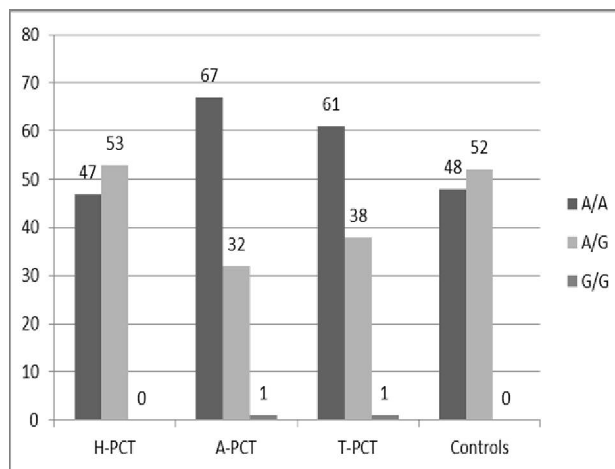

Figure 6. Genotype frequencies of m2 polymorphism (A/G)

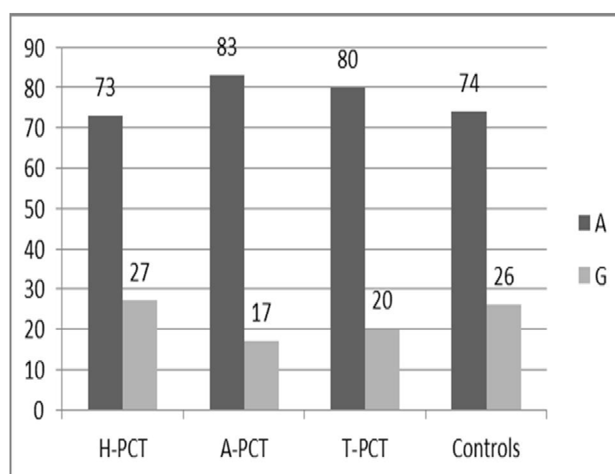

Figure 7. Allele frequencies of m2 polymorphism (A/G)

Applying vccSTATs program significant results are present in Table 4.

A-PCT vs Controls A/G vs A/A	H-PCT vs A-PCT A/G vs A/A
OR=0.45 0.24<CI<0.84	OR=2.36 1.02<IC<5.47
pf= 0.0090	pf=0.036
Protection genotype	**Risk genotype**

Table 4. Statistic with genotype frequencies.

<u>Haplotype Frequencies</u>

The haplotype estimated with the snpSTATs was C-G-C-C, only significative for H-PCT vs controls.
In the Table 5 are shown comparatively the results presented by Gardlo, Wickliffe [15,16] and this study.

CYP1A2				GF		AF	
study group	subtype of PCT	n	%C/C	% C/A	% A/A	%C	%A
Argentina	I & II	115	7	40	53	27	73
	I	77	9.0%	35	56	27	73
	II	38	3	50	47	28	72
	Controls	83	17	37	46	36	64
USA	I & II	66	5.8	39.1	55.1	25	75
	I	50	4	36	60	22	78
	II	16	13	56	31	41	59
	Controls	72	12.5	51.4	36.1	38	62
Denmark	I & II	53	5.7	22.6	71.7	17	83
	I	40	2.5	27.5	70	16	84
	II	13	15.4	7.7	76.5	19	81
	Controls	60	10	43.3	46.7	32	68
France	I & II	49	6.1	53.1	38.8	33	67
	I	45	ND	ND	ND	ND	ND
	II	4	ND	ND	ND	ND	ND
	Controls	48	12.5	47.9	39.6	37	64
Spain	I & II	102	2.9	49	48	28	73
	I	80	2.5	52.5	45	29	71
	II	22	4.5	36.5	59.1	23	77
	Controls	150	12	48	40	36	64
CYP1A1 m4				GF		AF	
study group	PCT subtype	n	% C/C	% C/A	%A/A	%C	%A
Argentina	I & II	111	67	29	4	81	19
	I	73	70	30	0	85	15
	II	38	60	26	14	74	26
	Controls	90	59	39	2	78	22
USA	I & II	71	97.2	2.8	0	98.6	1.4
	I	53	96	4	0	98	2
	II	16	100	0	0	100	0
	Controls	70	91.4	8.6	0	95.7	4.3
Germany	I & II	46	82.6	17.4	0	85.3	14.7
	I	29	89.7	10.3	0	94.8	5.2
	II	17	70.6	29.4	0	85.3	14.7
	Controls	101	92.6	7,4	0	100	0
CYP1A1 m2				GF		AF	
study group	PCT subtype	n	% A/A	% A/G	%G/G	%A	%G
Argentina	I & II	110	61	38	1	80	20
	I	78	67	32	1	83	17
	II	32	47	53	0	73	27
	Controls	93	48	52	0	74	26
USA	I & II	72	90	9	1	94	6
	I	ND	90	10	ND	95	5
	II	ND	100	ND	ND	100	ND
	Controls	ND	85	11	4	90	10

Table 5. Genotype and allele frequencies published by Wickliffe et al 2011, Gardlo 2003 et al. and our study.

IV. DISCUSSION

Previous reports have indicated that CYP1A21*F promotor variant A in intron 1 at nucleotide position -163 bp, increases the amount of the enzyme by augmenting its transcriptional activity and stability of the transcript [16]. Our results give us the same tendency and this will be related with the increase of the susceptibility to develop PCT. It is a rare case in which the polymorphic A allele is the more frequent in the studied population and others.

For CYP1A1, there is not previous report of the effect of m4 polymorphism and the susceptibility to develop this disease. The predict snp give rise that the aminoacid change will have not effect in the development of any pathology and the effect of nucleotide change could not be analyzed. Our studies showed that C allele (wt) is the more frequent and A allele was a risk factor to develop the PCT.

In the case of m2 polymorphism the A allele is the wt and is the more frequent. Previous reports have shown that the G variable (mutated) produces an aminoacid change increasing the CYP activity [13,20], ROS species and the susceptibility to develop cancer [12,13]. The same was demonstrated in our work for the PCT when we contrasted the H-PCT vs A-PCT groups for the genotype A/G vs A/A. In this case the increase of ROS would lead to the oxidation of uroporphyrinogen to uroporphomethene (competitive inhibitor) or to uroporphyrin (not metabolizable), being both risk factors to develop the Porphyria. Another alternative would be the direct oxidation of the cysteine, histidine and lysine in the active site of the enzyme. Instead, for A-PCT vs control group for the same genotypes previously contrasted, an unexpected result was obtained in which G allele could be a protection factor. We propose here that the xenobiotic itself would direct inhibit the enzyme.

For m1 polymorphism CYP1A1 (rs.4646903) in the 3' region the T6235C change increase the catalytic activity in China population [21]. In our case we have not significative differences in the contrasted groups for all genotypes and alleles but we need to increase the number of patients for a more secure statistic.

Other polymorphism of the CYP1A1 described in the literature is the m3: T5639C (intrón 7) only present in the African population.

For haplotype analysis with the snpSTATs contrasting each group of PCT vs Controls, only significative difference was found for H-PCT in which the risk haplotype was for m4-m2-m1-1A2: C-G-C-C.

All the differences found with other populations (Table 5) might be due to ethnicities differences among the various underling susceptibility factors to develop the PCT.

This is the first study of these polymorphisms in our population. We think that our results are relevant to Human health contributing in the future to prevent the development of the PCT.

ACKNOWLEDGEMENTS

The authors thank to H Muramatsu MD, Dr. MN Guolo, Dr. LM Oliveri and Mrs VI Castillo for their technical assistance.

Conflict of interest

The authors declare that they have no conflicts of interest concerning this article. No non-financial conflicts of interest exist for any of the authors.

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LIST OF ABBREVIATIONS

ALA δ -aminolevulinic acid
A-PCT Acquired PCT
AhR Aryl hydrocarbon receptor
Bp Base pair
CI Confidential interval
DNA Desoxirribonucleic acid
H-PCT Hereditary PCT
HCB Hexaclorobencene
HFE Hemochromatosis
H-PCT Hereditary PCT
OD Odds ratio
PBG Porphobilinogen
PCR Polymerase chain reaction
PCT Porphyria Cutanea Tarda
PPI Plasma Porphyrins Index
RFLP-PCR Restriction Fragment Length Polymorphism
ROS Reactive Oxygen Species
SNP Single nucleotide polymorphism
A-PCT Sporadic PCT
URO-D Uroporphyrinogen decarboxylase
UTP Urinary Total Porphyrins
Wt Wild type

Funding information

This work was supported by grants Q 289 (2014-2017) from UBA, PIP 049 (2012-2014), CO 528 (2014-2017) from CONICET and PID-BID PICT 3626 (2015) from ANPCyT.