

Identification of CYP3A5 and CYP2B6 Polymorphisms in Porphyria Cutanea Tarda Associated to Human Immunodeficiency Virus

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Abstract

To date, few or no data concerning the prevalence of polymorphisms in drug metabolism genes of antiretroviral drugs have been reported in the Argentinean population or in porphyric individuals worldwide. The purpose of the current investigation was to determine whether interindividual differences in cytochrome P450 3A5 (CYP3A) and 2B6 (CYP2B6) genes could influence the triggering of Porphyria Cutanea Tarda (PCT) in subjects with human immunodeficiency virus (HIV) after antiretroviral exposure.

A total of 141 subjects, 60 control volunteers and 81 unrelated individuals with PCT were included in the study. In the porphyric group, 21 individuals were HIV positive. To evaluate the presence of the alleles CYP3A5*3, CYP3A5*6 and CYP2B6*6 a polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis was performed.

The frequencies of CYP3A5*3 were 0.91 in control group, 0.89 in PCT patients and 0.89 in PCT-HIV. CYP2B6*6 frequencies were 0.31 in control group, 0.34 in PCT group and 0.30 in PCT-HIV group. We have shown that the allelic frequencies of CYP3A5*3 or CYP2B6*6 in our population were similar to those reported for other Caucasian populations.

Although, we have not found significant differences in polymorphisms of CYP3A5 and CYP2B6 between the different groups analyzed, there are an enormous number of biological variables that may influence antiretroviral treatment, like other genetic polymorphisms of phase I or phase II enzymes, or transporters like multidrug resistance transporter gene (MDR1), which can contribute to antiretroviral drug toxicities and response or even it is possible that the PCT-HIV association has more than one factor responsible for the onset of PCT symptoms.

Keywords: Human Immunodeficiency Virus; Polymorphisms; Porphyria Cutanea Tarda; CYP3A5; CYP2B6

Introduction

The cytochrome P450 (CYP) proteins are the major enzymes responsible for Phase I reactions in the metabolism of several drugs and synthesis of cholesterol, steroids and other lipids. Cytochrome P450 3A5 (CYP3A5) is a protein that in humans is encoded by the CYP3A5 gene. The CYP3A5 plays a major role in the metabolism of human immunodeficiency virus (HIV) protease inhibitors (PI) like indinavir and ritonavir [1]. Consequently, interindividual variation in the metabolism of CYP3A5 substrates is a factor in determining individual drug efficacy [2], and can result in clinically significant differences in drug toxicity and response [3,4]. Protease inhibitors have been associated with several adverse reactions like lipodystrophy syndrome, hypersensitivity reactions, urticaria, morbiliform eruptions, and a large number of drug interactions [5].

CYP3A5 is expressed in only 10–30% of adult human livers [6,7]. The main cause of variable expression of CYP3A5 has been attributed to the frequent single nucleotide polymorphisms (SNP) 6986A>G in intron 3, known as the CYP3A5*3 allele [3,8]. Another sequence variant that affects CYP3A5 expression is 14690G>A in exon 7, known as the CYP3A5*6 allele [3,4,9].

Cytochrome P450 2B6 (CYP2B6) is another member of the CYP family and makes up approximately 2–10% of the total hepatic CYP content. CYP2B6 is involved in the metabolism of efavirenz and nevirapine drugs, potent nonnucleoside reverse transcriptase inhibitors (NNRTI) for the treatment of HIV infection [10,11]. Inhibitors of reverse transcriptase have been associated with several adverse reactions like cutaneous eruptions, as well as a hypersensitivity syndrome [5].

Genetic polymorphisms in the CYP2B6 gene are common among Caucasian individuals and contribute to the extreme interindividual variability of CYP2B6 expression and enzymatic activity [12]. A frequent CYP2B6 variant, 516G>T, (CYP2B6*6) has been associated with a decreased clearance of plasma efavirenz and nevirapine [11,13–17] leading to adverse effects of these antiretroviral drugs.

Porphyria cutanea tarda (PCT) is the most common porphyria with a prevalence ranging from 1:5,000 to 1:25,000 [18]; while in Argentina it is 1:36,000 [19]. The disease usually occurs in adult life and it is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation, and hypertrichosis [20]. PCT is caused by subnormal activity of uroporphyrinogen decarboxylase (URO-D), the fifth enzyme of heme biosynthetic pathway. There are two main forms of PCT: type I (sporadic: s-PCT), most common, and type II (familial: f-PCT) [18,20] that could be differentiated by the erythrocyte URO-D activity [21]. There is also a form of familial PCT called type III, in which a family history of PCT

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is observed, but subnormal URO-D activity is restricted to the liver [22]. The clinical manifestation of PCT is frequently associated with exposure to precipitating agents, including polyhalogenated aromatic hydrocarbons, alcohol abuse, estrogen ingestion, iron overload, hepatitis C virus (HCV) and HIV infection and less frequently, hepatitis B virus (HBV) [19,23-25]. Data from Argentina reported a very high incidence of PCT-HIV association, showing 1:10 prevalence of HIV in our PCT patients [26]. However, since almost all the HIV infected patients with PCT had additional risk factors for Porphyria triggering, it is still unclear if HIV infection is actually a trigger for PCT [18, 23,25,27]. Despite this, there have been many reports that mentioned PCT triggering after or during the therapy with antiretroviral agents, even in the absence of a precipitating agent [5,28,29].

Although the widespread use of indinavir, ritonavir, nevirapine and efavirenz in the HIV treatment; the influence of CYP3A5 and CYP2B6 polymorphisms on these drugs metabolism, and its contribution to drug toxicity, no studies were reported in the Argentinean population and especially in the association PCT-HIV. The purpose of the current investigation was to determine whether interindividual differences in CYP3A5*3, CYP3A5*6 and CYP2B6*6 genotype could influence the onset of PCT in subjects with HIV after antiretroviral therapy.

Materials and Methods

All primers used for polymerase chain reaction (PCR) were synthesized by FAGO'S Laboratory (Buenos Aires, Argentina). All other chemicals and reagents were of molecular grade from Merck, Sigma, Promega, Ambion, BIO Labs and Amersham; Taq DNA polymerase was from Invitrogen. Digestion enzymes were from BIO Labs.

Subjects

A total of 141 subjects, 60 healthy volunteers and 81 unrelated PCT patients were included in the study. Among healthy volunteers, 44 were females and 16 males; and in the porphyric group 26 were females and 55 males. The porphyric group, previously studied in our Centre, had been diagnosed as PCT and among them, 21 individuals were HIV positive. In all cases, patients with PCT-HIV were asked about the antiretroviral treatment used, the onset date of the cutaneous symptoms, and any data that could be relevant to establish a causative association between antiretroviral agents and PCT triggering. All subjects have given their informed consent to participate in this study.

PCR studies

Genomic DNA was extracted from EDTA-collected whole blood samples by the GFX Genomic Blood DNA Purification Kit (Amersham).

For CYP3A5*3 and CYP3A5*6 polymorphisms, target DNA was amplified by PCR as described by Fukuen et al. [30] with slight modifications. The genotypes of each individual were determined using PCR-restriction fragment length polymorphism (RFLP) analysis. The primers used for analysis of CYP3A5*3 were: forward: CYP3A5 6956Fm; 5'-CTT TAA AGA GCT CTT TTG TCT CTC A-3' and reverse: CYP3A5 7155R; 5'-CCA GGA AGC CAG ACT TTG AT-3'. For analysis of CYP3A5*6 allele, the primers were: forward: CYP3A5 14505F; 5'-GTG GGT TTC TTG CTG CAT GT-3' and reverse: CYP3A5 14741R; 5'-GCC CAC ATA CTT ATT GAG AG-3'. The PCR reaction was carried out in 25 µl of solution consisting of 2.5 l of 10x PCR buffer, 0.2 mM of each dNTP, 0.4 µM of each primer, 100 ng of genomic DNA as a template, and 2.5 unit of Taq DNA Polymerase (Invitrogen). After initial denaturation at 95°C for 10 min,

amplification for the CYP3A5*3 or *6 alleles was performed using 37 cycles of 94°C for 30 sec, 56.5°C (*3 or *6) for 30 sec, and 72°C for 30 sec, followed by 72°C for 5 min for final extension in a THERM 1000, MaxyGene gradient thermal cycler (Axygen Scientific, USA). After PCR amplification, 10 µl of each PCR product (*3 or *6) was digested for a minimum of 16 h at 37°C with 5 units of DdeI. Electrophoresis was performed using a 3% agarose gel. For CYP3A5*3 amplifications, wild type DNA showed two fragments of 129 bp and 71 bp, whereas mutant PCR products in homozygosis resulted in three fragments of 107 bp, 71 bp and 22 bp (not visible) (Figure 1).

For CYP3A5*6 amplifications wild type DNA resulted in four fragments of 103 bp, 74 bp, 35 bp and 25 bp (the last two fragments were not visible), whereas mutant PCR products in homozygosis resulted in three fragments of 128 bp, 74 bp and 35 bp (not visible) (Data not shown).

For CYP2B6*6 polymorphism, target DNA was amplified by PCR as described by Lang et al. [12] with minor modifications. PCR reactions were performed in a total volume of 50 µl with 100 ng genomic DNA, 200 µM dNTPs, 2 pmol of primer forward: CYP2B6-4F5'GGTCTGCCCATCTATAAAC3' and primer reverse: CYP2B6-4R5'CTGATTCTTCACATGTCTGCG3', 2 mM MgCl₂, and 2.5 U Taq DNA Polymerase (Invitrogen). After 5 min of denaturation at 95°C, the PCR mixtures were subjected to the following conditions: 30 sec at 95°C, 30 sec at 54°C and 50 sec at 72°C for 30 cycles with a delayed last step of 10 min at 72°C in a THERM 1000, MaxyGene gradient thermal cycler (Axygen Scientific, USA) After PCR, 5 µl of product was digested with 5 units of restriction enzyme *BsrI* (New England Biolabs, Beverly, MA, USA) for 1 h at 60°C. Electrophoresis was performed using a 3% agarose gel. Wild type DNA resulted in three fragments of 241 bp, 268 bp and 17 bp (not visible), whereas mutant PCR products resulted in two fragments of 509 bp and 17 bp (not visible) (Figure 1).

Statistical analysis

Data were analyzed using the Fischer test. A p<0.05 was considered as significant.

Results

Data about age, gender, type of porphyria, total urinary porphyrins (TUP) or porphyrin plasma index (PPI) of PCT patients are shown in (Table 1). Among PCT patients, 67.9 % were men and 32.1% were women; within them, f-PCT group was constituted by 73.6% of men and 26.3% of women, while in s-PCT group, 58.6 % were men and 41.4 % were women. In the PCT-HIV group, all the individuals were s-PCT being 73.6 % men and 26.3 % women. In f-PCT, the onset age of the symptoms was 31 years while in s-PCT, it was 50 years and in PCT-HIV group 41 years. TUP mean values were 4.655 g/24 h for f-PCT, 6.099 µg/24 h for s-PCT and 9.706 µg/24 h for PCT-HIV patients. The IPP was 5.65, 4.64 and 6.4 for f-PCT, s-PCT and PCT-HIV patients respectively. Data about the date of infection with HIV and the antiretroviral therapy used, HCV coinfection and the therapy anti-HCV, the precipitating factors, and the onset date of the cutaneous symptoms in PCT-HIV group are shown in (Table 2). In patients that received antiretroviral therapy (76%), this treatment consisted of two IP plus one NNRTI, two NNRTI plus one nucleoside reverse transcriptase inhibitors (NRTI) or one IP, plus one NNRTI and one NRTI; in 24% of the individuals there are not available data or they received no treatment to date. Data about known potential precipitating factors showed that at present or in the past, 67% of this group is alcohol abuser, 19% received barbiturates, 57% consume abuse drugs, 67% is co-infected with HCV or more than one factor has been identified (43%), mainly HCV infection and alcohol

intake. Porphyrin symptoms were skin lesions, blisters, pigmentation, hypertrichosis, cutaneous fragility and dark urine was present in the majority of the individuals.

Genotype distribution of CYP3A5 and CYP2B6 alleles observed in healthy subjects and porphyric patients are shown in (Table 3).

Results showed that 18.3% (11/60) of control group, 22.7% (13/60) of PCT and 23.8% (5/21) of PCT-HIV were heterozygotes for CYP3A5*3 allele. Homozygous CYP3A5*3 alleles were detected in 81.7% (49/60) of control group, 78.3% (47/60) of PCT patients and 76.2% (16/21) of PCT-HIV patients. The CYP3A5*6 allele was not found in any of the subjects analyzed. CYP2B6*6 allele was detected in heterozygosity in 48.3% (29/60) of control group, 48.3% (29/60) of PCT and 57.1% (13/21) of PCT-HIV patients.

When CYP2B6*6 allele was studied, a 6.7% (4/60) of healthy group and 10% (6/60) of PCT was present in homozygosity. No homozygous individuals were found in PCT-HIV group. No significant differences in genotype distribution respect to control group in any of the alleles analyzed was found.

The allelic frequencies of CYP3A5*3 and CYP2B6*6 are shown in (Table 4). In control group CYP3A5*3 allele have a frequency of 0.91 in control group, 0.89 in PCT patients and 0.88 in PCT-HIV patients. CYP2B6*6 frequency was 0.31 in control group, 0.34 in PCT group and 0.29 in PCT-HIV group. There was not significant differences respect to control group in any of the alleles analyzed.

Data	PCT n= 60		PCT-HIV n= 21
Type of PCT	f-PCT n=19	s-PCT n=41	s-PCT n=21
Age (years)			
Mean value	31	50	41
Range	(7-61)	(27-77)	(26-59)
Gender			
M	14	24	17
F	5	17	4
TUP (µg/24h)			
Mean value	4,655	6,099	9,706
Range	(765-14,388)	(1,250-14,802)	(1,464-22,156)
PPI			
Mean value	5.65	4.54	6.4
Range	(1.80-10.30)	(1.80-8.60)	(2.10-9.30)

f-PCT: Familial PCT; s-PCT: Sporadic PCT; M: male; F: female
Normal values: TUP: Total urinary porphyrins: 20-250 µg/24 h; PPI: Plasma porphyrin index : ≤ 1.30

Table 1: Biochemical data of porphyric group.

Data total n= 21	Data n (%)	No data n (%)	No therapy n (%)
HIV infection: Date of diagnostic	≥ 10 years = 10 (48) < 10 years = 4 (19)	7 (33)	No data
Antiretroviral therapy	16 (76)	4 (19)	1(5)
PCT onset: Date after diagnostic	≥ 2 years = 6 (29) < 2 years = 7 (33)	8 (38)	No data.
HCV coinfection	14 (67)	7 (9.5)	No data
	With treatment 6 (43) No Treatment 8 (57)		
Drugs intake:			
Alcohol intake	14 (67)	No data	No data
Barbiturate intake	4 (19)		
Other abuse drugs intake	12 (57)		

Experimental conditions are described in Materials and Methods

Table 2: Data of PCT-HIV group.

Polymorphism	Genotype	Healthy n=60	PCT n=60	PCT-HIV n=21
CYP3A5*3 6986A>G	AA	0	0	0
	AG	11 (18.3%)	13 (21.7%)	5 (23.8%)
	GG	49 (81.7%)	47 (78.3%)	16 (76.2%)
CYP3A5*6 14690G>A	GG	60 (100%)	60 (100%)	21 (100%)
	GA	0	0	0
	AA	0	0	0
CYP2B6*6 516G>T	GG	27 (45.0)	25 (41.7)	9 (42.9)
	GT	29 (48.3)	29 (48.3)	12 (57.1)
	TT	4 (6.7)	6 (10.0)	0

Experimental conditions are described in Materials and Methods

Table 3: Genotype distribution.

Alleles	Healthy n=120	PCT n=120	PCT-HIV n=42
CYP3A5*3	0.91	0.89	0.89
CYP2B6*6	0.31	0.34	0.29

Experimental conditions are described in Materials and Methods

Table 4: Frequency of CYP2D6 alleles.

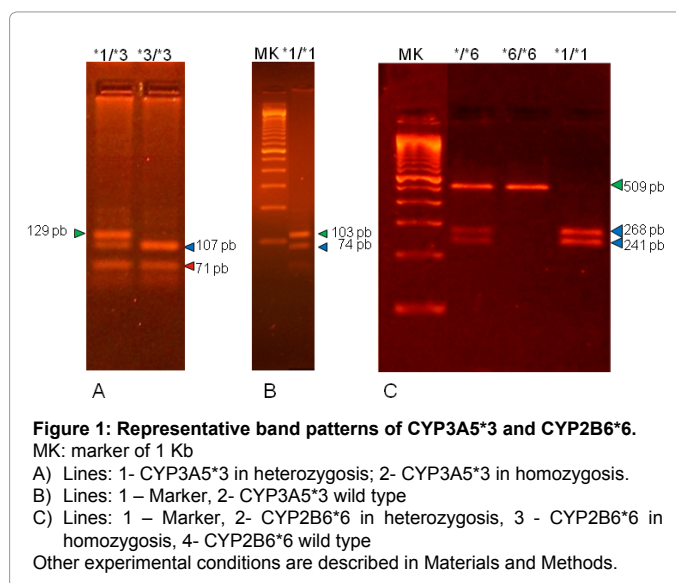


Figure 1: Representative band patterns of CYP3A5*3 and CYP2B6*6. MK: marker of 1 Kb
A) Lines: 1- CYP3A5*3 in heterozygosity; 2- CYP3A5*3 in homozygosity.
B) Lines: 1 – Marker, 2- CYP3A5*3 wild type
C) Lines: 1 – Marker, 2- CYP2B6*6 in heterozygosity, 3 - CYP2B6*6 in homozygosity, 4- CYP2B6*6 wild type
Other experimental conditions are described in Materials and Methods.

Discussion

Porphyria cutanea tarda (PCT) is the most common of the human Porphyrias. Association between PCT and HIV infection has been frequently reported [23,24,28]. Several adverse cutaneous reactions have been observed after the therapy with protease and reverse transcriptase inhibitors [5]. The search for a linkage between the triggering factors in the PCT-HIV association and the implementation of molecular diagnosis testing on individual CYP polymorphisms before drug treatment is indeed very important to make possible the avoidance of the side effects of antiretroviral drugs and the highly possible manifestation of the PCT symptoms.

In this work, we have studied all the available PCT group who attended our Center for diagnosis and porphyria control during the last year. The relationship between males and females of this group is lower than that found in our total PCT population. According to previous studies [26,27], biochemical data indicated that total urinary porphyrins are more elevated in PCT-HIV group than in non HIV PCT patients.

Because CYP3A5 may represent up to 50% of the total hepatic CYP3A content, this gene would be the most important genetic

contributor to interindividual and interracial differences in CYP3A-dependent drug clearance. Detection of CYP3A5 variant alleles, and knowledge about this allelic frequency in the population, will be extremely useful to optimize pharmacotherapy [31].

To date, few or no data concerning prevalence of polymorphisms in drug metabolism genes of antiretroviral drugs have been reported in the Argentinean population or in porphyric individuals worldwide.

In our analysis we found that CYP3A5*3 allele was present with a frequency of 91% in the control group, with 83% in the homozygosis form. We have shown that the allelic frequency of CYP3A5*3 in our population was similar to that reported for other Caucasian populations (91.7%) [31]. Larriba et al. [32] in an Argentinean group of renal transplanted subjects found that 89% of the individuals analyzed were homozygotes and 11% were heterozygotes for the allele CYP3A5*3. In this work, the frequency was different from studies of African American, Hispanic [33] and Japanese patients [33]. Fukuen et al. [30] reported that the homozygous wild (*1/*1) genotype of CYP3A5*3 was found to be more common in African-American, intermediate in Japanese but rare in Caucasian populations. Van Schaik et al. [31] found that only one individual was homozygous wild type for CYP3A5*3 in a group of 500 healthy Dutch Caucasians. In agreement with these data, the wild type (*1/*1) allele for CYP3A5*3 was not found in any of the groups analyzed in the present work.

The analysis of CYP3A5*6 allele showed that none of the subjects studied was carrying this allele. These data are coincident with the results found by Solas et al. [36], who showed in a piece of work carry out in a French population, that nobody was carrying the CYP3A5*6/*6 genotype, confirming its very low frequency in the Caucasian population.

When CYP2B6*6 allele was analyzed, the frequency observed in the healthy group was 32%. This value was a little higher than that reported for other Caucasian populations (28.6%) [35].

Melito et al. [28] suggested that the high incidence of PCT associated with HIV in Argentinean patients might be caused by exposure to potential precipitating factors such as alcohol, drug abuse and/or infection with hepatitis viruses, and not to a direct role of HIV infection on porphyrin metabolism. In agreement with this theory, Drobacheff et al. [24] proposed that there are abnormalities in porphyrin metabolism associated with HIV infection, but they rarely constitute a real profile of PCT. Other hypotheses suggest that the virus may act at different levels altering porphyrin metabolism [23]. On the other hand, there are several reports that relate antiretroviral exposure and drug toxicities to the triggering of PCT [5,26]. Moreover, Celesia et al. [29] have reported the development of PCT during therapy with tipranavir/ritonavir although the patient did not use alcohol or drugs.

Results here presented demonstrated for the first time, that CYP3A5*3 allele have a frequency of 0.89 in both PCT and PCT-HIV groups; and that CYP2B6*6 allele showed a frequency of 0.34 and 0.29 in PCT and PCT-HIV subjects respectively. These frequencies are similar to those reported for other Caucasian control populations.

Although, we have not found significant differences in polymorphisms of CYP3A5 and CYP2B6 between healthy, PCT and PCT-HIV groups, there are a great number of biological variables that may influence antiretroviral treatment. There are other genetic polymorphisms of Phase I or even of Phase II enzymes, or transporters like the multidrug resistance transporter gene (MDR1) [37], which can contribute to antiretroviral drug toxicities and response or even it is possible that the PCT-HIV association has more than one factor

responsible for the onset of PCT symptoms. In a somehow similar study it was reported recently, in humans, the increased frequency of the CYP1A2-g-163A allele in s-PCT smoker patients, leading to the significant earlier onset of the clinical overt disease [38].

Therefore, larger genotyping studies should be performed to determine the incidence of other genetic polymorphisms affecting antiretroviral treatment for HIV, to elucidate the exact relationship in PCT triggering in HIV individuals.

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