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Cytochrome P450 *CYP2B6*6* distribution among Congolese individuals with HIV, Tuberculosis and Malaria infection

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ABSTRACT

Background: The cytochrome P450 *CYP2B6*6* (*CYP2B6* c.516G>T; rs3745274) is one of the genetic factors that alters the drug metabolism in antimalarial, antiretroviral and TB first-line drugs. In Central African populations, the distribution of the *CYP2B6*6* variant is poorly documented. This study investigated the distribution of *CYP2B6* c.516G>T variant among Congolese individuals.
Methods: A total of 418 patients with HIV-1 mono-infection, HIV-1 and Tuberculosis coinfection and symptomatic *P. falciparum* malaria were genotyped for the *CYP2B6* c.516G>T SNP using Restriction Fragment Length Polymorphism (RFLP). The allele frequencies and genotype distributions were determined.
Results: The *CYP2B6* c.516G>T was successfully analysed in 69% (288/418) of the study participants. Among the investigated individuals, the distribution of the major allele *CYP2B6**G was 45% and the minor *CYP2B6**T allele was 55%. Significant differences in genotype distribution were also observed among the studied individuals. The *CYP2B6**GG (rapid metabolizer) genotype was observed in 17% (49/288) followed by *CYP2B6**GT (intermediate metabolizer) 55% (159/288) and *CYP2B6**TT (poor metabolizers) 28% (80/288).
Conclusion: This study contributes to increasing understanding on population pharmacogenetics and may help policy makers regulate treatment guidelines in the Congolese population with a high burden of HIV, Malaria and TB.

Introduction

Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis (TB) and Malaria are the leading causes of mortality in Africa. In 2017, a decline in the number of deaths related to these diseases was reported (MOH, 2017). This milestone is, in part, attributed to the prudent use of effective drugs. The emergence and spread of drug-resistant pathogens threaten to reverse these gains. Combined drug therapy has been widely adopted to circumvent this public health bottleneck. The artemisinin combined therapy (ACT) has been adopted as the first-line antimalarial drug, replacing ineffective first-line drugs such as chloroquine (CQ) and Sulfadoxine-Pyrimethamine (SP). The combination of artesunate (AS) with amodiaquine (AQ) is one of the most widely used ACT regimens. In Republic of Congo, the treatment guideline is the prescription of artesunate–amodiaquine (ASAQ) and artemether-lumefantrine (AL) as first-line and second-line drugs respectively, for the treatment of acute uncomplicated malaria (Ministère de la Santé et de la Population, 2006).

In 2007, Republic of Congo introduced free antiretroviral treatment (ART) for the management of HIV/AIDS within its National Strategic Framework (NSF). Unfortunately, due to delay and/or unavailability of antiretrovirals, there exists a frequent interruption in treatment regimens (Santé, 2013). Efavirenz (EFV), a non-nucleotide reverse transcriptase inhibitor (NNRTI)

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combined with two other nucleoside reverse transcriptase inhibitors (NRTIs), is the preferred first-line treatment for HIV/AIDS (Usach et al., 2013).

Genes involved in drug metabolism are important determining factors for drug efficacy and toxicity (Masebe et al., 2012; Michaud et al., 2012; Tozzi, 2010). Cytochrome P450 (CYP) enzyme is an essential enzyme in modulating the drug metabolism. Several single nucleotide polymorphisms (SNPs) had been identified in the *CYPs* and are associated with altered enzymatic activity thus causing treatment failures (Zanger and Schwab, 2013; Zhou et al., 2009). The human *CYP2B6* is involved in the metabolism of several antibiotics, antimalarial and TB-first line drugs and antiretroviral drugs (Simonsson et al., 2003; Ward et al., 2003). The *CYP2B6* gene is highly polymorphic (Lang et al., 2001) and is characterized by a large inter-individual variability in world populations (Zhou et al., 2017). The functionally characterized *CYP2B6* genetic variants contribute to altered drug metabolism, and differential plasma concentrations, thus individuals being either classified as poor or fast metabolizers (Telenti and Zanger, 2008). The *CYP2B6* genetic variants were documented as useful predictors of pharmacokinetics and drug response (Rakhmanina and van den Anker, 2010). Analysis of these SNPs can be useful to improve drug efficacy and could reduce potential drug toxicity, prior to treatment.

The frequency of the *CYP2B6* SNPs varies also across different ethnicities (Arnaldo et al., 2013; Zhou et al., 2017). Among the studied *CYP2B6* variants, the *CYP2B6 c.*516G>T (rs3745274) and *CYP2B6 c.*785A>G (rs2279343) are more frequent among African ethnicities and are less frequent among Caucasian and Asian populations (King & Aberg, 2008). The *c.*516G>T SNP (rs3745274) causes abnormal splicing, decreased expression and activity of the *CYP2B6*6* (Hofmann et al., 2008). In Africa, the prevalence of *CYP2B6* c.516G>T (rs3745274) ranges from 36 to 60% (Klein et al., 2005; Mehlotra et al., 2006; Nyakutira et al., 2008). Rifampicin (RMP) and Isoniazid (INH) are used as first-line drugs for TB treatment. *CYP2B6* is also involved in the metabolism of RMP and INH (Yimer et al., 2011). The *CYP2B6* c.516G>T polymorphism was shown to modulate the TB therapeutic response (Fernandes et al., 2015). The *CYP2B6 c.*516G>T has been associated with an increased plasma exposure to EFV (Cortes et al., 2013; Sinxadi et al., 2015; Swart et al., 2013) and increased risk of toxicity in the CNS (Aurpibul et al., 2012; Martin et al., 2014; Sinxadi et al., 2015).

To the best of our knowledge, there is a scarcity of data on the distribution of *CYP2B6* c.516G>T (rs3745274) especially in Central African population. In this context, this study aimed to determine the *CYP2B6* c.516G>T of allele frequencies and genotypes in a cohort of patients who were receiving antimalarial, antiretroviral and TB-first line drugs.

Materials and methods

Ethical approval and consent

Ethical approval was obtained from the Institutional Ethics Committee of the Fondation Congolaise pour la Recherche Médicale. Written informed consent was obtained from the study participants and from parents/guardians in case of children, prior to recruitment.

Study subjects

A total of 418 participants were enrolled in this study (Figure 1). The 418 enrolled subjects were classified in two groups. Among the

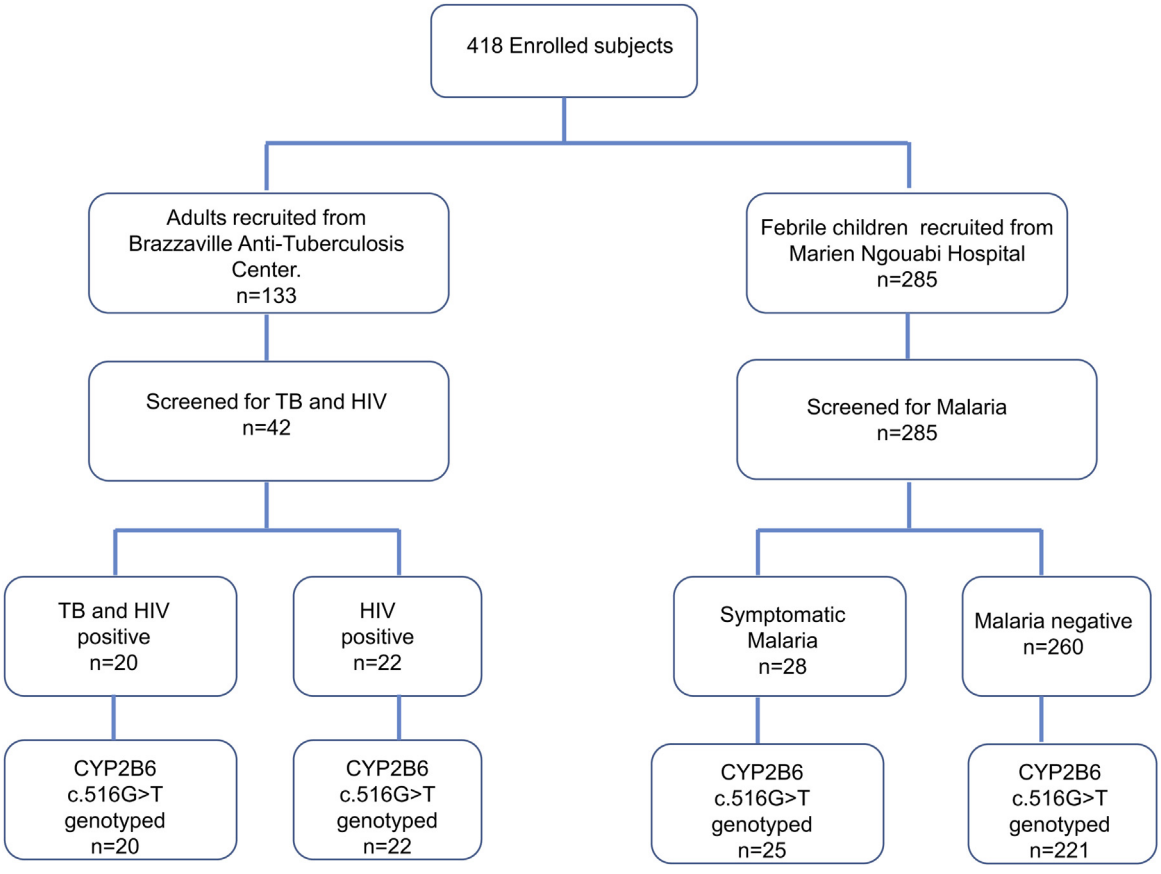

Figure 1. Clinical characteristics of the recruited patients in this study cohort.

418 enrolled, 133 were adult patients recruited from Brazzaville anti-Tuberculosis Centre. The remaining 285 participants were children aged between one and ten years old presenting with fever (≥37.5 °C) at the paediatric ward of the Marien Ngouabi Hospital in Northern Brazzaville, Republic of Congo. Of the 133 recruited, 42 adults were screened for TB and HIV. Among the 42 adults, 20 were positive for both HIV and TB, whereas 22 were positive for HIV alone. Among the 285 febrile children attending the paediatric ward, 28 had symptomatic malaria and 257 were asymptomatic. Two ml of venous blood was collected in EDTA tubes and were transported in cooling cycles and stored under optimal conditions until further use. The baseline data of recruited patients are illustrated in Table 1.

CYP2B6*6 *genotyping*

Genomic DNA was purified from peripheral whole blood samples preserved with EDTA using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following manufacturer's instructions. The c.516G>T of the *CYP2B6*, located in exon 4 of *CYP2B6*, was genotyped using restriction fragment length polymorphism (RFLP), as described previously (Lang et al., 2001). Briefly, PCR reactions were conducted in a total volume of 50 μl containing 100 ng genomic DNA, 200 μM of dNTPs, 2 pmol of the CYP2B6-4F and CYP2B6-4R primers, and 2.5U Taq polymerase (Promega Corporation). PCR products (5 μl) were digested with BsrI (New England Biolabs Beverly, MA, USA) for 15 min at 60 °C and resolved in a 2% agarose gel stained with SYBR Green. The restricted PCR fragment revealed three different genotypes at different product sizes. The *CYP2B6* c.516GG (wild-type) showed two bands (241 and 268 bp), followed by *CYP2B6* c.516GT (heterozygous) with three bands (241 bp + 268 bp +509 bp) and the *CYP2B6* c.516TT (homozygous mutant) with 509 bp. In order to confirm the methodological approach, twenty representative samples were subjected to Sanger sequencing to confirm the respective genotypes.

Data analysis

Data were analysed by STATA v.9.1 (STATA Corporation, Texas, USA) and the level of significance was set at $P < 0.05$. Genotype frequencies were determined by simple gene counting and by using the expectation-maximum (EM) algorithm. Chi-square test was executed to determine the differences in allele and genotype distributions between the different sub groups of patients. The significance of deviation from Hardy-Weinberg equilibrium was tested using the random-permutation procedure as implemented in the Arlequin v. 3.5.1.2 software (http://cmpg.unibe.ch/software/arlequin3/).

Results

The *CYP2B6* c.516G>T was successfully genotyped among 288/418 (69%) of the enrolled study subjects. The distribution of alleles and genotypes in different study groups is given in Table 1. The distribution of the *CYP2B6* genotypes were in Hardy-Weinberg equilibrium ($P = 0.05$). The Congolese individuals had a high frequency of genotypes that contribute to intermediate and poor response to treatment (CYP2B6 c.516GT: 55% and CYP2B6 c.516TT: 28% respectively). The genotype distribution was also similar among individuals, when stratified for different infections. The CYP2B6 c.516T allele remains a major allele in the Congolese population.

Discussion

There is a paucity of data on the distribution of *CYP2B6* c.516G>T variant in the Central African population. This study aimed to determine the *CYP2B6* c.516G>T genotype and allele frequencies in patients who were receiving antimalarial, antiretroviral and TB-first line drugs. This first study reports that most of the Congolese individuals carry those *CYP2B6* genotypes that modulate the pharmacokinetics of the drugs routinely prescribed such as Rifampicin, Isoniazid, Efavirenz and ACTs.

The Hap Map database reports that the G and T alleles are segregated in sub-Saharan African population as 0.62 and 0.37 respectively. However, when compared to the NCBI Hap Map database, the frequency of the observed SNP variant *CYP2B6* c.516G>T (rs3745274) in our study revealed a higher proportion of T variant in the Congolese population compared to that of the wildtype G allele (*CYP2B6* c.516G = 0.45 and *CYP2B6* c.516T = 0.55).

In Africa, the overall frequency of the G and T alleles is 65% and 35%, respectively, and that of genotypes GG is 42%, GT is 45%, and TT is 13% (Scibona et al., 2015). Arnaldo et al. demonstrated a large variation in the distribution of different *CYP2B6* variants in Mozambique including the G516T substitution (Arnaldo et al., 2013). In this study, we observed a higher frequency of *CYP2B6* c.516G>T variant in Congolese individuals than those reported from previous studies from African countries (Arnaldo et al., 2013; Gounden et al., 2010; Mukonzo et al., 2009; Nyakutira et al., 2008; Paganotti et al., 2015; Sinxadi et al., 2015; Staehli Hodel et al., 2013). This might be due to a selective pressure and a frequency dependent selection occurring at this locus. Alternatively, heterogeneity among different ethnic populations in this geographical region cannot be excluded (Gounden et al., 2010; Klein et al., 2005; Kwara et al., 2009; Mehlotra et al., 2006; Nyakutira et al., 2008). Corroborating our findings, studies from Uganda and Zimbabwe document a high frequency of the studied *CYP2B6*6* variant (66–68%) (Rajman et al., 2017).

CYP2B6 c.516G>T is considered to be an independent predictor of EFV plasma concentrations in HIV-infected patients. EFV plasma concentrations <1 mg/L were associated with an increased risk of virological failure, possibly leading to potential drug resistances and poor treatment outcome. Concentrations >4 mg/l are associated with an increased risk for central nervous system (CNS) impairment and liver toxicity (Marzolini et al., 2001; Zakeri et al., 2014). Few other studies also demonstrate the absence of this

Table 1
CYP2B6 c.516G>T allele and genotype distribution among Congolese patients with HIV and/or TB positive and with malaria.

CYP2B6 c.516G>T	All individuals (n = 288)	HIV and/orTB coinfection (n = 42)	Symptomatic malaria (n = 25)	Non malarial fever (n = 221)	P value
Mean age in years (range)	8 (1–54)	36,7 (14–54)	4 (1–10)	3 (1–10)	P < 0,001
Male/female ratio	148/139	18/23	14/11	113/108	P < 0,001
NP 1					
GG/rapid (%)	49 (17)	11 (26)	3 (12)	35 (16)	
GT/intermediate (%)	159 (55)	17 (41)	14 (56)	128 (58)	
TT/poor (%)	80 (28)	14 (33)	8 (32)	58 (26)	
Allele G (%)	257 (45)	39 (46)	20 (40)	198 (45)	NS
Allele T (%)	319 (55)	45 (54)	30 (60)	244 (55)	

correlation (Fumaz et al., 2005; Read et al., 2009; Takahashi et al., 2007). Previous reports show that CNS side effects occur within the first week of EFV treatment following EFV treatment with the recommended dose (600 mg/per day) and may persist for a long period of time (Dhoro et al., 2015; Vo and Varghese Gupta, 2016). In South Africa, Hong Kong, China, Cambodia and Thailand, elevated EFV plasma concentrations were observed among HIV patients with the CYP2B6 516TT genotype (Pressiat et al., 2017). Nonetheless, genotyping of *CYP2B6* c.516G>T serves as a valuable tool for identifying HIV positive individuals who are most likely to develop CNS side effects following EFV treatment (Swart et al., 2015; Swart et al., 2013). In our study, the frequency of genotype 516TT (poor metabolizer) among HIV-1 positive individuals was higher (27,3%) than in Mozambique, South Africa, Burundi, Ethiopia and Tanzania (Arnaldo et al., 2013; Calcagno et al., 2012; Ngaimisi et al., 2013; Sinxadi et al., 2015). However, the distribution of genotype 516TT was in accordance as observed in Cameroon (Paganotti et al., 2015). Taken together, the distribution of the studied *CYP2B6* c.516G>T variant may thus help to determine the predictability of EFV concentrations in naïve African patients with HIV.

In Congo, TB-HIV co-infection is 29% and an estimated HIV prevalence is at 3% in the general population (PNLT, 2014). In fact, disease course and a high mortality are influenced by coinfections (Dolin et al., 1994). Although the treatment is free, TB remains a public health burden in the Republic of Congo, esp. in a population living with HIV (MOH). Efavirenz and Rifampicin are the first line treatment prescribed to HIV/TB patients. Since rifampicin is a potential inducer of CYP expression, co-administration with EFV is hypothesized to cause rapid EFV metabolism which may lead to sub-therapeutic EFV plasma concentrations (Breen et al., 2006). However, several studies have rejected this hypothesis (Borand et al., 2014; Kwara et al., 2011; Manosuthi et al., 2013; Ramachandran et al., 2009). In fact, two previous studies reported a subtle increase of EFV plasma concentration in African and African-American patients following EFV-rifampicin treatment (Gengiah et al., 2012; Luetkemeyer et al., 2013). Co-administration of first-line TB drugs are associated with drug induced hepatotoxicity (Xiang et al., 2014; Yimer et al., 2011; Fernandes et al., 2015) Rifampicin (RMP) and Isoniazid (INH) are widely used combination regimens and were shown to associate with hepatotoxicity in TB patients with *CYP2B6* c.516TT genotype (Fernandes et al., 2015). In this context, our findings suggest that 40% (8/20) of participants (*CYP2B6* c.516TT) with HIV-1 + TB co-infection in this study may likely develop drug induced hepatotoxicity if RMP and INH are administered together. This also implies that co-administration of EFV and RMP would subject these patients to additional side effects as a result of poor drug metabolism and evaluated EFV plasma concentrations (Yimer et al., 2008).

Malaria caused by *P. falciparum* is also a public health concern in Republic of Congo, especially among young children. In Republic of Congo, the national drug policy recommends artesunate–amodiaquine (ASAQ) and artemether–lumefantrine (AL) for the treatment of acute uncomplicated malaria (Ministère de la Santé et de la Population, 2006). The human *CYP2B6* gene is also involved in the metabolism of artemisinin and its derivatives (Simonsson et al., 2003), The *CYP2B6*6* allele is associated with increased plasma concentrations of artemisinin and artemether (Kerb et al., 2009). The children with symptomatic malaria infection were also genotyped for *CYP2B6*6*. The high frequency of the *CYP2B6*6* homozygous mutant allele (32%) indicates that a large proportion of individuals in this group might be poor metabolizers of artesunate (Kerb et al., 2009; Marwa et al., 2014), resulting in an increased risk to toxicity of the above anti-malarial drugs (Marwa et al., 2014).

Due to poor resource settings, investigations were carried out only to understand the differential distribution of specific *CYP2B6* c.516G>T genotype among Congolese individuals with comorbidities. Although other loci in CYP450 enzymes are also involved in modulating the bioavailability of the drugs, this is considered to be a limitation of this study.

Conclusion

A larger number of infected patients in the study is desirable to confirm the distribution of the *CYP2B6*6* allele and to correlate the genetic findings with the treatment outcome. This first study from Republic of Congo provides a basic understanding on the distribution of *CYP2B6* c.516G>T variant and has important repercussions in determining treatment guidelines in a population with a high burden of HIV, Malaria and TB.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

FN and FKK designed the study. SMP and NGS participated in the study design, performed the experiments. FKK supervised the study procedures. CV, DN and TPV analysed the data. FN was responsible of overall study. All authors participated in drafting the manuscript.

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