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Prevalence of Cytochrome P450 2B6 Single Nucleotide Polymorphism in an HIV-Positive Cohort in Jos, Nigeria: Implication for HIV Therapy

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Abstract

Background: Africans exhibit great diversity in cytochrome P450 2B6 isoenzyme (CYP2B6), the major enzyme in efavirenz metabolism.

Aim: We examined the frequency of two functional single nucleotide polymorphisms (SNPs) of the CYP2B6 pharmacogene in HIV-infected Nigerians on efavirenz-based antiretroviral therapy. The potential implications of the SNPs for HIV therapy were discussed.

Materials and Methods: A cross-sectional study conducted from July 2018 to December 2018 in a tertiary health facility in Nigeria. A random sample of a clinic cohort of HIV-infected adult Nigerians of different ethnicities was characterized for two key SNPs; CYP2B6:516G>, and CYP2B6:983T > C, defining the alleles CYP2B6*6 and CYP2B6*18, respectively. Hardy–Weinberg equilibrium was calculated to evaluate the genotype frequency distribution.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

There are no conflicts of interest.

Results: Genotyping was successful for 262 (83%) of the 316 study participants. Of those with genotype results, mean age was 41 ± 8 years and 182 (69.5%) were female. The CYP2B6:516 G/G (extensive metabolizers), CYP2B6:516 G/T (intermediate metabolizers), and CYP2B6:516 T/T (poor metabolizers) genotype frequency was 35.9%, 46.6%, and 17.6%, respectively. Also, 88.9% and 11.1% of participants were carriers of the CYP2B6:983 T/T and CYP2B6:983 T/C (poor metabolizers) genotypes, respectively. There were no gender or age-related differences in the genotype distribution. The CYP2B6:516G >T allele frequencies showed no significant deviations from the Hardy-Weinberg equilibrium ($P = 0.66$).

Conclusions: The intermediate metabolizer genotype was more common than the extensive and poor metabolizer genotypes in our study sample. We recommended further studies to investigate the risk of efavirenz underexposure and overexposure in carries of the extensive and poor metabolizer genotypes respectively in our patient population.

Keywords

Antiretroviral therapy; pharmacogenomics; CYP2B6; efavirenz

Introduction

Cytochrome *P450 2B6* (*CYP2B6*) is the main enzyme involved in the metabolism of efavirenz,[1–4] a non-nucleoside reverse HIV transcriptase inhibitor used as part of the initial treatment regimen of HIV infection in adults and adolescents in Nigeria.[5] The CYP2B6 isoenzyme is also involved to a lesser extent in the metabolism of nevirapine a non-nucleoside reverse transcriptase inhibitor.[5] The gene encoding the CYP2B6 isoenzyme is highly polymorphic with more than 38 alleles, and over 100 single nucleotide polymorphisms (SNPs) described.[6] Among different variants of the CYP2B6 gene, the CYP2B6*6 (516 G >T, 785 A >G) and CYP2B6*18 (983 T>) haplotypes leads to reduced catalytic activity and a significant decrease in protein expression.[7] Clinically, the CYP2B6 516 G >T variant allele of the CYP2B6*6 haplotype, and CYP2B6:983 T >C variant of the CYP2B6*18 haplotype are associated with elevated plasma concentrations of efavirenz in different ethnicities.[8–10] Based on the effect of CYP2B6 polymorphisms on efavirenz trough concentration, patients are stratified into different phenotypes.[11] The CYP2B6 slow metabolizer genotype is defined by either 516 T/T homozygosity, dual 516 G/T–983 C/T heterozygosity, or 983 C/C homozygosity, while their absence is characteristic of the extensive metabolizer phenotype. The intermediate metabolizers are defined by 516 G/T heterozygosity.[11] Clinically, increased efavirenz concentration in plasma, cerebrospinal fluid, breast milk, and hair common in slow metabolizers is associated with increased efficacy (decreased viral load, increased T-cell count), CNS side effects, and hepatic injury.[12–21] Also, QTc prolongation;[22] and discontinuation of efavirenz therapy had been reported in carriers of the poor metabolizer genotype.[23,24]

The CYP2B6*6 allele, characterized by two amino acid changes, Gln172His and Lys262Arg, occurs at a considerably greater frequency in people of African ancestry compared to Asians and Caucasians.[25] In a review of several African genomic studies, the reported frequency of the CYP2B6*6 allele ranged from 17% to as high as 60% in various African populations.[26] In Nigeria, the CYP2B6*6 allelic frequency of 38%, 42%,

and 42% was reported among Ibos, Hausas, and Yorubas.[27] The CYP2B6*18 (983 T >C) haplotype is uncommon in Asians and Caucasians but occurs at a low frequency of 4–9% in people of African ancestry.[10]

The great genetic diversity of the CYP2B6 gene makes it difficult to extrapolate findings from one population to another. Given the clinical importance of CYP2B6*6 and CYP2B6*18 haplotypes in the metabolism of efavirenz,[8–10] an anti-HIV medicine widely used in Nigeria and other Sub-Saharan African countries, it is crucial to conduct locally relevant pharmaco-epidemiological studies to inform clinical and programmatic decision. Data on the frequency of the CYP2B6*6 and CYP2B6*18 haplotypes in the HIV infected population in Nigeria are sparse. We aimed to describe the frequency of two key functional SNPs, CYP2B6:516G >T (rs3745274), and CYP2B6:983T >C (rs2839949), defining the alleles CYP2B6*6 and CYP2B6*18, respectively, in HIV-positive Nigerians residing in North Central Nigeria. We also discussed the potential implications of the SNPs on efavirenz-based therapy in HIV-infected patients.

Materials and Methods

Study setting

Jos University Teaching Hospital (JUTH), a tertiary health institution located in North-Central Nigeria, has close to two decades of experience in the provision of HIV treatment, care, and support for people living with HIV. As of December 2018, over 7,000 patients were on antiretroviral therapy (ART) at the study site, with 51%, 31%, 13%, and 5% of them on efavirenz, nevirapine, atazanavir, and lopinavir-based ART respectively.

Study design and population

In a cross-sectional study conducted from July 2018 to December 2018, HIV-positive adult Nigerians of mixed ethnicity were characterized for two key functional single nucleotide polymorphisms (SNPs), CYP2B6:516G >T (rs3745274, CYP2B6: Gln172His), and CYP2B6:983T >C (rs28399499, CYP2B6: Ile328Thr), defining the alleles CYP2B6*6 and CYP2B6*18 respectively. The candidate genes were chosen based on reports in the literature, as well as their prominence in decreased enzyme expression and association with high plasma drug concentrations in patients treated with efavirenz.[22,28–32]

Included participants were aged 18 years and above, treated with efavirenz-based ART for more than one year at the study site.

Sampling procedure and sample size determination

Study participants were selected by a systematic random sampling technique. With the utility of a clinic appointment list, a triage Nurse selected ten patients who met the inclusion criteria on each clinic day. Eligible patients who consented to participate in the study were consecutively recruited until the study sample size was reached. The sample size was determined using OpenEpi epidemiological calculator and the method by Kelsey *et al.*, (1996).[33] A sample size of 316 was utilized based on the formula for sample proportions

with a finite correction factor and a hypothesized CYP2B6:516G >T SNP prevalence of 30%+/−5.[27,34]

Data collection

Baseline socio-demographic and clinical information was obtained from an electronic medical record system maintained at the clinic (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA).[35]

Genomic DNA extraction and genotyping procedure

Buffy coat preparation—A phlebotomist drew venous blood samples from each participant. The collected blood was transferred into labeled EDTA tubes and centrifuged at 800 x g for 10 minutes at room temperature (15–25°C) with brake offs to remove a concentrated leukocyte band (buffy coat). The collected buffy coat was stored at minus 80°C in a well-labeled 2-ml Cryovial until further analysis.

DNA extraction: DNA extraction—Total genomic DNA was isolated from the buffy coat using a modified salting-out method.[36] Quick-DNA™ Universal Kit (Zymo Research Corp), which uses spin-column technology, was used for DNA extraction. Briefly, the steps involve cell Lysis (guanidinium thiocyanate + proteinase-k), purification (genomic binding buffer [Isopropanol] + Zymo-Spin™ IIC-XL Column), washing, and dry spin for ethanol-free DNA (pre-wash buffer [low concentration of guanidinium thiocyanate]), and DNA elution (DNA elution buffer- tris (hydroxymethyl) aminomethane at pH 8–9). The DNA extraction was performed at the APIN-supported laboratory of Jos University Teaching Hospital. The APIN-supported laboratory is an ISO 15189 accredited laboratory.

Sequencing for SNP—Sequencing was done at Inqaba Biotec™ laboratories in Pretoria, South Africa. Sequencing was performed using the Agena Mass ARRAY System, 384/96 Genotyping (Agena Bioscience, Inc. San Diego, CA, USA). The genotyping analysis was performed based on the manufacturer recommendation with reagents included in the iPLEX Gold SNP genotyping kit and the software and equipment provided with the MassARRAY platform. In brief, sequencing with the iPLEX Gold technology, which has been fully described elsewhere,[37] consists of an initial locus-specific PCR reaction, followed by a single base extension (SBE) using mass-modified dideoxynucleotide terminators of an oligonucleotide primer, which anneals immediately upstream of the polymorphic site of interest. The sequences (5’ to 3’) for the forward and reverse primers for the CYP2B6:516G>T variant are ACGTTGGATGTTCTTCCTAGGGGCCCTCAT and ACGTTGGATGTGATCTTGGTAGTGGAATCG respectively, while for the CYP2B6:983T>C variant the forward and reverse primers are ACGTTGG ATGTCTGTACAGAGAGAGTCTAC and ACGTTGGATGGTGTATGGCATTTTGGCTCG, respectively. The product of these reactions was directly applied to a silicon chip. The mass of the extended primer was determined using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry.[38] The mass of the primer indicates the mutation of interest, and the mass of added bases indicate the alleles present at the polymorphic site. A software (SpectroTYPER) automatically translated the mass of the observed primers into a genotype for each reaction.

Ethical consideration

Jos University Teaching Hospital ethical committee (Ref: JUTH/DCS/ADM/127/XXVII/826) and APIN Public Health Initiative (Ref: OHRP IRB# IRB00011406) approved the study protocol, while Harvard T.H. Chan School of Public Health approved the use of secondary data. Study participants gave informed written consent. All study procedures were per the Helsinki Declaration of 1975, as revised in 2000.

Statistical analysis

Participants' characteristics were described in frequencies and proportions for categorical variables, while numeric variables were described by median or mean depending on the distribution. The frequency distribution of the alleles and observed frequency of the genotypes were tabulated. The genotype frequency distribution in the studied population was compared with the Hardy–Weinberg equilibrium based on the Chi-square (χ^2) test of observed versus expected using the Stata version 13 (College Station, TX, USA).

Results

Participants' characteristics

In all, 262 (83%) of the 316 participants' samples were successfully genotyped. Characteristics of participants with genotype results summarized in Table 1 indicate that most were female, middle-aged adults in their forties, married, had secondary education, and self-employed. Clinically, a little below half of the participants tested positive for the hepatitis B virus at ART initiation. Most participants had been on ART for more than five years (range 1–14 years), and the majority had CD4 cell count above 400 (range 31–1253) cells per mm^3 at the time of the study.

Genotype frequencies

The genotype frequencies reflected in Figure 1 shows that the GG (extensive metabolizers), GT (intermediate metabolizers), and TT (poor metabolizers) genotypes of CYP2B6:516G >T variant alleles were present in 35.9%, 46.6%, and 17.6% of participants, respectively. For the CPY2B6:983 T > C variant, the TT and TC genotypes were present in frequencies of 88.9% and 11.1%, respectively. There were no gender, age, or ART duration-related differences in the distribution of genotypes [Table 2].

The CYP2B6*6 genotypes and allele frequencies showed no significant deviations from Hardy-Weinberg equilibrium in the Nigerian populations ($P = 066$) [Table 3].

Discussion

We described the frequency of CYP2B6:516 G >T and CYP2B6:983T >C variant alleles in a mixed ethnic HIV positive population of Nigerians residing in northern Nigeria. The intermediate metabolizer genotype (CYP2B6 516 G/T) was more common in the studied population than the extensive (CYP2B6 516 G/G), and poor (CYP2B6 516 T/T) metabolizers. The CYP2B6*6 genotypes and allele frequencies showed no significant deviations from Hardy-Weinberg equilibrium in the Nigerian populations.

We reported genotype frequencies of the CYP2B6:516 G >T variant allele among Nigerians residing in the North comparable to the frequency of 40.3%, 46.0%, 13.7% for the GG, GT, and TT genotypes respectively among HIV-positive Nigerians residing in southwest Nigeria.[34,39] Other African studies[40–43] had reported frequencies of *CYP2B6:*516 G >T comparable to those reported in this study.

Clinically, the extensive metabolizer phenotype which is prevalent in our studied population is associated with subtherapeutic plasma concentrations of efavirenz in HIV-1 infected patients.[44] A 50–70% probability of developing a sub-therapeutic trough level of efavirenz had been reported in children carrying the CYP2B6 516 G/G genotype in an earlier study.[45] Given the large population of Nigerian patients treated with efavirenz-based ART, and the high prevalence of the extensive metabolizer genotype, it is crucial to investigate subtherapeutic drug level exposure in our patient population.

The intermediate metabolizer genotype (CYP2B6 516 G/T) was more common than other genotypes in our patient sample. This genotype is associated with a slight but not significant reduction in hepatic CYP2B6 protein expression and activity, with no significant variation in efavirenz plasma concentration in carriers of the genotype.[46] In one study, the proportion of those with sub-therapeutic concentrations of efavirenz was comparable (19% versus 20%) among carriers of the heterozygous genotype (CYP2B6 516 G/T) and the wild-type genotype (CYP2B6 516 G/G).[44]

The poor metabolizer TT genotype of CYP2B6:516G > T observed in 18% of our studied population is associated with higher efavirenz plasma concentration and increased central nervous system side effects.[15–17] However, some studies failed to demonstrate an improved or worsened clinical response in individuals with higher efavirenz concentrations.[41,47] Interestingly, in some studies, the slow metabolizer phenotype was associated with increased efficacy (decreased viral load, increased T-cell count) of efavirenz therapy.[12–14] The mechanism of increased efficacy reported in previous studies [12–14] is not clear, but there exists the possibility that the higher efavirenz concentrations in slow metabolizers may offset the adverse impact of the relatively lower efavirenz concentrations in the event of suboptimal adherence.[48]

The CYP2B6:983T >C variant, the defining SNP of the *18 allele,[49] occurred at a low frequency in our studied population. This is the first report on the frequency of the CYP2B6:983T >C variant allele in the Nigerian population. The frequency of 11% observed in our study is slightly higher than the frequency of 4–9% observed in Black or African Americans and 1.1% in Hispanic Americans.[9,25,50] Also, the variant was not observed in Paupa New Guinea, Asians, and Caucasians.[9,25,50] Carriers of the heterozygous TC genotype of the CYP2B6:983T >C variant allele are slow metabolizers and the presence of the genotype is associated with high plasma drug concentrations in patients treated with efavirenz.[9,10] In a study to address the challenge of increased drug toxicity associated with high levels of efavirenz in slow metabolizers, the dose of efavirenz was adjusted down for slow metabolizers.[51] The study found that even at the lower doses, viral loads remained suppressed while central nervous system side effects were reduced. Larger studies are needed to validate this tailored approach to efavirenz dosing before its wider application.

One potential limitation of our study is the risk of survival bias, as patients included in the study were those on long-term efavirenz therapy owing to a programmatic shift towards ART initiation with delutegravir containing regimen at the time of the study. Our estimate of CYP2B6*6 could be biased either toward or away from the null depending on if the slow metabolizer genotype confers either an advantage or disadvantage for survival in HIV patients on efavirenz. The randomness of our sample minimized the risk of selection bias.

Conclusion

The intermediate metabolizer genotype (CYP2B6 516 G/T) was more common in our studied population and comparable to other African populations. However, the presence of the rapid and poor metabolizer phenotypes in our studied sample implies that about 36% and 20% of HIV-infected persons on efavirenz therapy in our setting are potentially at risk of drug underexposure and overexposure respectively. The long-term survival implications of the rapid and poor metabolizer phenotypes prevalent in Nigerians and other Africans merits further investigations.

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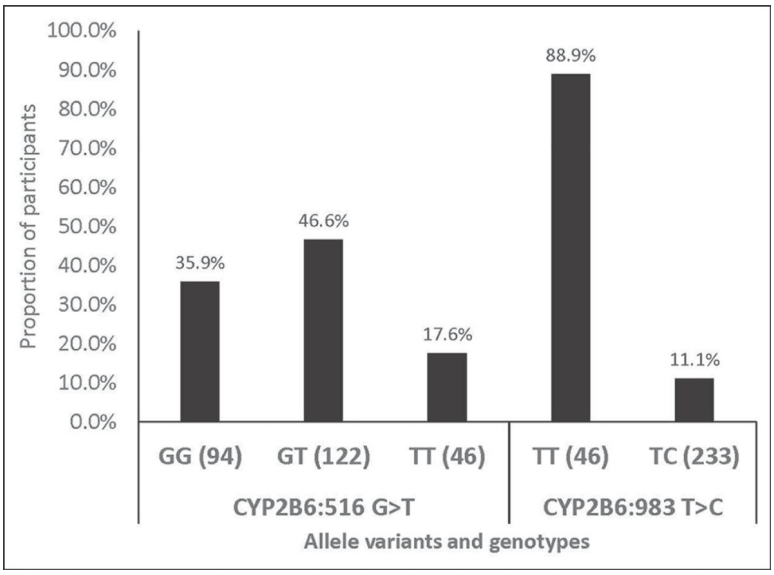

Figure 1:

CYP2B6:516 G > T and CYP2B6:983 T > C genotype frequencies in people living HIV in North Central Nigeria. Number in parenthesis represents the number of participants with genotype

Table 1:

Demographic and clinical characteristics of study participants (n=262)

Characteristics	Subgroup	Frequency	Percentage
Sex	Female	182	69.5
	Male	80	30.5
Age in years	Mean±standard deviation	41 ± 8	
Marital Status	Single	28	10.7
	Married	208	79.4
	Divorced/Separated	15	5.7
	Widowed	11	4.2
Highest Education	No formal education	7	2.7
	Primary	29	11.1
	Secondary	157	59.9
	Tertiary	69	26.3
Occupation	Government	7	2.7
	Private	30	11.5
	Self-employed	178	67.9
	Student	5	1.9
	Unemployed	42	16.0
Baseline hepatitis B virus status	Negative	137	52.3
	Positive	125	47.7
Baseline hepatitis C virus status	Negative	250	95.4
	Positive	12	4.6
ART duration, years	Median (IQR)	6.17 (5.8–11.5)	
CD4 cell count cells/cm^3 (last measurement)	Median (IQR)	457 (332.5–561.5)	

ART:Antiretroviral therapy, IQR:Interquartile range

Table 2:

Genotype frequency according to participants' characteristics

Characteristics	Distribution of CYP2B6:516G >T variant			*P*	Distribution of CYP2B6:983T >C variant		*P*
	GG*	GT†	TT‡		TT	TC*	
	Number (%) with genotype				Number (%) with genotype		
Sex							
Female	66 (36.26)	89 (48.9)	27 (14.84)	0.19	159 (87.36)	23 (12.64)	0.22
Males	28 (35)	33 (41.25)	19 (23.75)		74 (92.5)	6 (7.5)	
Age, years, mean±SD	42.63±8.93	40.15±7.84	40.71±7.78	0.91	41.06±7.77	41.72±11.81	0.69
ART duration, years, median (IQR)	6.42 (5.84–11.64)	6.01 (5.75–10.7)	6.22 (5.85–11.49)	0.23	6.22 (5.84–11.53)	5.91 (5.57–8.68)	0.14
Genotype frequency	94 (35.9)	122 (46.6)	46 (17.6)		233 (88.9)	29 (11.1)	

*Extensive metabolizers

†Intermediate metabolizers

‡Poor or slow metabolizers, SD=Standard deviation, ART=Antiretroviral therapy, IQR=Interquartile range

Table 3:

Genotype frequency compared with Hardy-Weinberg equilibrium*

Phenotype	*CYP2B6516* G>T genotype	Observed	Expected	Chi-square (*P*)
Extensive metabolizer	GG	35.9	33.6	0.85 (0.66)
Intermediate metabolizer	GT	46.6	48.7	
Poor metabolizers	TT	17.6	17.6	
Minor allele	(T)		42	

*Hardy-Weinberg equilibrium. $P^2 + 2Pq + q^2=1$ and P + q=1, where, p=Frequency of the dominant (major) allele in the population. q=Frequency of the recessive (minor) allele in the population. p2=Percentage of homozygous dominant individuals. q2=Percentage of homozygous recessive individuals. 2pq=Percentage of heterozygous individuals