


Distribution of alleles, genotypes and haplotypes of the *CYP2B6* (rs3745274; rs2279343) and *CYP3A4* (rs2740574) genes in the Malian population

Implication for pharmacogenetics

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Abstract

Cytochrome P450 enzymes play a central role in the phase I biotransformation process of a wide range of compounds, including xenobiotics, drugs, hormones and vitamins. It is noteworthy that these enzymes are highly polymorphic and, depending on the genetic makeup, an individual may have impaired enzymatic activity. Therefore, the identification of genetic variants in these genes could facilitate the implementation of pharmacogenetic studies and genetic predisposition to multifactorial diseases. We have established the frequencies of *CYP2B6* (rs3745274; rs2279343) and *CYP3A4* (rs2740574) alleles and genotypes in 209 healthy Malian subjects using TaqMan drug metabolism genotyping assays for allelic discrimination. Allele frequencies were 37% for *CYP2B6* rs3745274; 38% for *CYP2B6* rs2279343; and 75% for *CYP3A4* rs2740574 respectively. Overall, the frequencies observed in Mali are statistically comparable to those reported across Africa except North Africa. The major haplotypes in *CYP2B6* rs3745274 and *CYP2B6* rs2279343 were represented by GA (60.24%) followed by TG (35.36%). We noted a strong linkage disequilibrium between *CYP2B6* rs3745274 and *CYP2B6* rs2279343 with $D' = 0.91$ and $r^2 = 0.9$. The frequencies of the genotypic combinations were 43.5% (GT/AG), 37.3% (GG/AA) and 11.5% (TT/GG) in the combination of *CYP2B6*-rs3745274 and *CYP2B6*-rs2279343; 26.8% (GT/CC), 25.4%, (GT/CT), 17.2% and GG/CT in the combination *CYP2B6*-rs3745274-*CYP3A4*-rs2740574; 26.8% (AG/CC), 23.9% (AA/CC), 19.1% (AG/CT), and 11% (AA/CT) in the combination *CYP2B6*-rs2279343-*CYP3A4*-rs2740574, respectively. The most common triple genotype was GT/AG/CC with 24.9%, followed by GG/AA/CC with 23.9%, GT/AG/CT with 16.7%, and GG/AA/CT with 10%. Our results provide new insights into the distribution of these pharmacogenetically relevant genes in the Malian population. Moreover, these data will be useful for studies of individual genetic variability to drugs and genetic predisposition to diseases.

Abbreviations: CE = Ethic Committee, CYP450 = Cytochrome P450, EDCTP = European and Developing Countries Clinical Trials Partnership, EDTA = Ethylenediaminetetraacetic acid, FAPH = Faculty of Pharmacy, FMOS = Faculty of Medicine and Odontostomatology, ICER = International Center of Excellence in Research, SNP = Single Nucleotide Polymorphism, SPATOMA = Study of pharmacogenetics of ARVs treatment outcomes in Mali, West Africa, TMA = Training Mobility Action, UCRC = University Clinical Research Center, USTTB = University of Sciences, Techniques and Technologies of Bamako.

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1. Introduction

Cytochrome P450 (CYP450) enzymes are a superfamily of hemoproteins involved in phase I of the metabolism drugs and many other xenobiotics, thus playing a vital role in protecting the body against toxic derivatives from harmful compounds.^[1] In fact, the biotransformation reactions carried out by CYP450 allow the body to protect itself against the occurrence of cancers and the toxic effects of drugs or even other endogenous or exogenous substances such as hormones and vitamins, thus contributing substantially to the body's homeostasis^[2]; In mammals, CYP450 is expressed with a much higher concentration in the liver, but also to a lesser extent in the small intestine, lung and the kidney.^[3,4] It has been reported that 90% of the metabolism process are driven by CYP450 1–4 families.^[5] In addition, CYP450 is known to be highly polymorphic and, depending on genetic background, these enzymes can affect the pharmacokinetics and pharmacodynamics of drugs at the individual level, thus explaining interindividual genetic differences in response to drugs.^[6–8] The human CYP450 superfamily consists of 18 families, 42 subfamilies with 59 active genes.^[9] Among these, the *CYP2B6* and *CYP3A4* families have been widely explored in genetic association studies for multifactorial diseases such as gout,^[10] acute myeloid leukemia,^[11] chronic obstructive pulmonary disease^[12] as well than in pharmacogenetic studies including antiretrovirals (nevirapine, efavirenz),^[13] antimalarial (artemisinin),^[14] anticancer (chronic myeloid leukemia)^[15] and anesthetics (propofol).^[16] The *CYP2B6* and *CYP3A4* genes are located on the long arms of chromosomes 19q13.2 and 7q22.1 respectively.^[17,18] Several single nucleotide polymorphisms (SNPs) have been identified in these genes at the exonic, intronic, and promoter regions. Some of these variants classified as loss-of-function greatly increase the plasma concentrations of substrates, while the others classified as a gain-of-function reduce plasma concentrations.^[19] It was reported that the replacement of G by T at position 516 of the *CYP2B6* gene resulting in a Glutamine–Histidine change reduces significantly the catalytic activity of the gene. In addition, several studies have noted that the *CYP2B6* rs3745274 homozygous mutant genotype is associated with increased plasma concentrations of efavirenz, leading to side effects related to the central nervous system.^[20,21] However, the *CYP2B6* rs2279343 which leads to the change from Lysine to Arginine at position 262 induces a lower plasma exposure to efavirenz.^[22] The SNP rs2740574 in *CYP3A4* promoter increases the activity of *CYP3A4* and seems to be associated with the metabolism of tacrolimus requiring dose readjustments.^[23] It is important to stress that the allelic distribution of these genes varies from one population to another around the world, thus displaying strong interindividual, interethnic and geographical disparities.^[24] To the best of our knowledge, these data are missing for the Malian population. In addition, Mali is a tropical country where AIDS and malaria are major public health problems. It should be mentioned that most of the drugs used to treat these conditions are primarily metabolized by CYP450. For this reason and given the clinical importance of these genes encoding CYP450, we carried out the present study in order to establish the allelic and genotypic frequencies of *CYP2B6* in exons 4 and 5 (rs3745274, [Q172H]; rs2279343, [K252R]) and *CYP3A4* in the promoter (rs2740574) in our healthy population. The data from this study will be used to better design genetic association studies such as individual susceptibility to multifactorial diseases or variability in drug response.

2. Materials and methods

2.1. Study participants

The study protocol was approved by the Ethics Committee of the Faculty of Medicine and Odontostomatology (FMOS)/Faculty of Pharmacy (FAPH), University of Sciences, Techniques and Technologies of Bamako (USTTB) under the number 2018/113/CE/FMPOS. All participants received a detailed explanation of the study protocol before agreeing to sign the informed consent. For molecular biological purposes, five milliliters of peripheral venous blood were collected from each participant in a tube containing EDTA as an anticoagulant and stored at -20°C at the laboratory of the International Center of Excellence in Research-Mali (ICER, Mali). In sum, we recruited 209 healthy and unrelated subjects, including 120 female and 89 male from August 2018 to January 2019. The study participants recruited at the Department of Infectious and Tropical Diseases, University Hospital Center of Point G.

2.2. *CYP2B6* (rs3745274, rs2279343) and *CYP3A4* (rs2740574) genotyping

Genomic DNA was isolated from white blood cells using the Gentra Puregene Blood Kit according to the manufacturer's instructions. Reagents for TaqMan drug metabolism genotyping assays for allelic discrimination (Applied Biosystems Genotyping Assays) were used to establish the genetic profile of study participants. The following assays identification numbers were used: C_7817765_60 rs3745274 for *CYP2B6*, C_1837671_50 rs2740574 for *CYP3A4* rs2740574, a custom designed TaqMan assay was performed for *CYP2B6* rs2279343. The 7500 Fast Real-Time PCR System (Applied Biosystems) was used to genotype the different SNPs. PCR mixture consisted of a 5 µl TaqMan master mix (2X), 0.5 µl TaqMan drug metabolism genotyping assays mix (20X), and 1 µl of DNA completed to 10 µl with nuclease free water. The PCR run method was as follows: an initial step at 60°C for 30s, hold stage at 95°C for 10 min followed by 40 cycles: step 1 at 95°C for 15s and step 2 at 60°C for 1 min supplemented by a read stage at 60°C for 30s.

2.3. Statistical analysis

The SPSS version 16 statistical package (SPSS Inc., Chicago, IL, USA) was used to assess the frequencies of *CYP2B6* rs3745274, rs2279343) and *CYP3A4* (rs2740574) in our population. The chi-square (X^2) test was used to check whether the distribution of alleles is in Hardy–Weinberg equilibrium or not. We compared the frequencies observed in Mali with the frequencies of other populations with the same test. Analysis of pairwise linkage disequilibrium between SNPs in *CYP2B6* was performed using SNPstats.^[25] A *P*-value less than .05 was considered statistically significant.

3. Results

In the present work, we established the allele and genotypic frequencies of the *CYP2B6* and *CYP3A4* genes in 209 healthy Malian subjects using the TaqMan genotyping method. Our study group was composed of 57.4% women and 42.6% men with a mean age of 30.5 ± 11.9 years (range 18–78 years). Table 1 displays the distribution of the three SNPs in the Malian population, The profiles of the genotypes observed in the

Table 1
Allelic and genotypic profiles of CYP2B6-rs3745274, CYP2B6-rs2279343 and CYP3A4 rs2740574 in 209 Malian subjects.

Genes/SNPs	Genotypes/Alleles	All Participants, N (%)	Male, N (%)	Female, N (%)	P
CYP2B6* 6/ rs3745274	GG	83 (40)	40 (45)	43 (36)	.32*
	GT	96 (46)	39 (44)	57 (48)	
	TT	30 (14)	10 (11)	20 (17)	
	G	262 (63)	119 (67)	143 (60)	
	T	156 (37)	59 (33)	97 (40)	
	HWE: P	.77	1	.85	
CYP2B6* 4/ rs2279343	AA	80 (38)	39 (44)	41 (34)	.32†
	AG	100 (48)	40 (45)	60 (50)	
	GG	29 (14)	10 (11)	19 (16)	
	A	260 (62)	118 (66)	142 (59)	
	G	158 (38)	60 (34)	98 (41)	
	HWE: P	.88	1	.85	
CYP3A4/ rs2740574	CC	120 (57)	49 (55)	71 (59)	.83‡
	CT	74 (35)	33 (37)	41 (34)	
	TT	15 (7)	7 (8)	8 (7)	
	C	314 (75)	131 (74)	183 (76)	
	T	104 (25)	47 (26)	57 (24)	
	HWE: P	.46	.78	.61	

* $\chi^2=2.27$.
 † $\chi^2=2.3$.
 ‡ $\chi^2=0.37$.

CYP2B6 gene were 40% (GG), 46% (GT), and 14% (TT) in exon 4; 38% (AA), 48% (AG), and 14% (GG) in exon 5, respectively. In CYP3A4 gene, the genotypes observed were 57% for CC, 35% for CT and 7% for TT. The minor allele frequencies were 37%, 38%, and 25% for CYP2B6-rs3745274, CYP2B6-rs2279343 and CYP3A4 rs2740574, respectively. We found no deviations from the Hardy–Weinberg equilibrium in the SNPs examined. The distribution of CYP2B6, and CYP3A4 was statistically comparable between males and females. Major haplotypes identified from exons 4 and 5 in the CYP2B6 gene were observed in subjects carrying GA (60.24%) and TG (35.36%), while minor haplotypes were found in individuals harboring GG with 2.44% or TA with 1.96% (Fig. 1). A strong linkage disequilibrium was observed between the two SNPs in CYP2B6 with $D' = 0.91$ and $r^2 = 0.9$. The frequencies of the different genotype combinations are summarized in Figure 2. When analyzing the combinations of double genotype we noted in genotypes 1 and 2 (CYP2B6-rs3745274-CYP2B6-rs2279343), that 43.5% of the participants carried the heterozygous profile GT/AG, followed by the bearers of the homozygous wild-type

profile GG/AA with 37.3% and 11.5% harboring the homozygous mutant TT/GG profile. The most frequent combinations in genotypes 1 and 3 (CYP2B6-rs3745274-CYP3A4-rs2740574) were represented by GT/CC (heterozygous/homozygous wild-type) with 26.8%, GG/CC (both homozygous wild-type) with 25.4%, GT/CT (both heterozygous) with 17.2% and GG/CT (homozygous wild-type/heterozygous) with 11%, respectively. Compared to this, a similar pattern of inheritance of the combined genotypes was observed in genotypes 2 and 3 (CYP2B6-rs2279343-CYP3A4-rs2740574) with 26.8% of subjects harboring AG/CC, 23.9% for AA/CC, 19.1% for AG/CT, and 11% for AA/CT. In terms of the combination of the three genotypes, we observed that 24.9% of our participants simultaneously inherited the GT/AG/CC genotypes, followed by GG/AA/CC with 23.9%, GT/AG/CT with 16.7%, and GG/AA/CT with 10%. Of the 209 participants, the triple genotype frequencies associated with impaired enzymatic activities were 5.3% for subjects harboring the TT/GG/CT profile, 4.3% for TT/GG/CC, and 1.9% for TT/GG/TT.

4. Discussion

One of the major challenges of the twenty-first century for researchers and clinicians is to be able to predict the therapeutic outcomes of an individual for a given drug on the one hand and, on the other hand, to understand the development of multifactorial diseases. CYP450 is well known to be involved in the metabolism of many drugs as well as in the development of multifactorial diseases. This is the first time that the distribution of CYP2B6-rs3745274, CYP2B6-rs2279343 and CYP3A4-rs2740574 has been established in Malian healthy subjects. The frequency of the CYP2B6-rs3745274 mutant T allele observed in the Malian population was 37%, which is comparable to those observed in Central Africa (Cameroon 37%),^[26] East Africa (Tanzania) 34%,^[26] South Africa 36%^[26] and in West African countries including Ivory Coast (38%),^[27] Nigeria (36.3%),^[28] and Ghana (46%).^[29,30] Looking at data

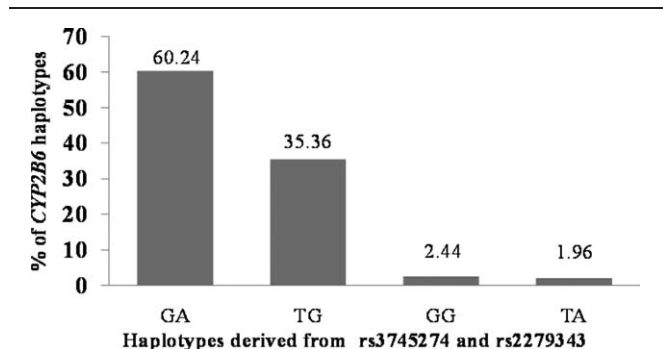


Figure 1. Haplotypes distribution of CYP2B6-rs3745274 and CYP2B6-rs2279343 in the Malian population.

	Genotypes 1;2		Genotypes 1;2;3	
		N (%)		N (%)
CYP2B6-rs3745274¹	GT/AG	91 (43.5)	GTAGCC	52 (24.9)
	GG/AA	78 (37.3)	GGAACC	50 (23.9)
	TT/GG	24 (11.5)	GTAGCT	35 (16.7)
	TT/AG	6 (2.9)	GGAACT	21 (10)
	GG/AG	3 (1.4)	TTGGCT	11 (5.3)
	GT/GG	3 (1.4)	TTGGCC	9 (4.3)
	GG/GG	2 (1)	GGAATT	7 (3.3)
	GT/AA	2 (1)	GTAGTT	4 (1.9)
CYP2B6-rs2279343²	GT/CC	56 (26.8)	TTAGCT	4 (1.9)
	GG/CC	53 (25.4)	TTGGTT	4 (1.9)
	GT/CT	36 (17.2)	GTGGCC	3 (1.9)
	GG/CT	23 (11)	GGAGCC	2 (1)
	TT/CT	15 (7.2)	GGGGCC	2 (1)
	TT/CC	11 (5.3)	TTAGCC	2 (1)
	GG/TT	7 (3.3)	GGAGCT	1 (0.5)
	GT/TT	4 (1.9)	GTAACC	1 (0.5)
CYP3A4-rs2740574³	TT/TT	4 (1.9)	GTAACT	1 (0.5)
	AG/CC	56 (26.8)		
	AA/CC	50 (23.9)		
	AG/CT	40 (19.1)		
	AA/CT	23 (11)		
	GG/CC	14 (6.7)		
	GG/CT	11 (5.3)		
	AA/TT	7 (3.3)		
AG/TT	4 (1.9)			
GG/TT	4 (1.9)			

Figure 2. Distribution of combined genotypes between *CYP2B6*-rs3745274, *CYP2B6*-rs2279343 and *CYP3A4*-rs2740574.

from North Africa, we found that the frequency observed in Mali was statistically higher than that reported in Egypt (28.8%) $P = .03$,^[31] but lower than that observed in the Moroccan population (55.5%) $P = .000$.^[15] As for *CYP2B6*-rs2279343, the frequency of the mutant G allele was 38% in the Malian population. This frequency was almost comparable to the frequencies reported in other African countries such as Egypt 30.4%,^[31] Cameroon 35%,^[26] and South of Africa 36%^[26] (Table 2). The frequencies of *CYP2B6* in exons 4 and 5 reported in the European and Asian population were slightly lower than those observed in Mali.^[26] Overall, the minor allele frequencies for both *CYP2B6*-rs3745274 and *CYP2B6*-rs2279343 observed in Mali were similar to the frequencies reported in the 1000Genomes project for the African population.^[32] We noted a high LD between the two SNPs in *CYP2B6* gene, showing their proximity. The frequencies of haplotypes in the Malian population were comparable to those observed in Cameroon and South African.^[26] It has been reported that the *CYP2B6*-rs2279343 variant is associated with an increase protein expression with strong enzymatic activity, and that the opposite effect is observed with the *CYP2B6*-rs3745274 variant.^[31,33] In our analysis, we noticed in genotypic combination 1;2 that approximately 43.5% of our participants carried heterozygous genotypes while subjects harboring normal and mutated homozygous genotypes were 37.3% and 11.5%, respectively.

These results could suggest a compensatory effect between these two SNPs which also exhibit strong linkage disequilibrium. The involvement of these SNPs of *CYP2B6* gene in the metabolism of various drugs has been demonstrated by several studies.^[14,34] Efavirenz and nevirapine (two non-nucleotide reverse transcriptase inhibitors) are among the flagship drugs whose metabolism is influenced by *CYP2B6* SNPs. In fact, the association between high plasma concentrations of drugs leading to side effects on the central nervous system and the presence of the *CYP2B6* rs3745274 polymorphism has been reported in HIV patients receiving efavirenz, while the *CYP2B6* rs2279343 polymorphism has been found to be associated with increased metabolic activities with low plasma exposure.^[22] Thus, the genotyping of these SNPs in our HIV-positive patients could allow better therapeutic management while limiting the occurrence of central nervous system related side effects. In addition, the drugs prescribed to treat cases of malaria are currently artemisinin-based combinations and these are metabolized by *CYP2B6* genes. Carriers of *CYP2B6*-rs3745274 variant have been reported to undergo a drug interaction when efavirenz and lumefantrine are co-administered, resulting in decreased plasma lumefantrine concentrations. AIDS and malaria are common in Mali; therefore, establishing the genetic profile of *CYP2B6* in our HIV patients infected with malaria parasite will facilitate better classification of patient according to their genotypes and

Table 2**Distribution of CYP2B6-rs3745274, CYP2B6-rs2279343 and CYP3A4-rs2740574 in different African populations.**

Populations	N	rs3745274T (%)	rs2279343G (%)	rs2740574C (%)	References
West Africa					
Malian (this study)	209	37	38	75	Present study
Ivory Coast	41	38	–	–	[27]
Nigeria	150	36.3	–	–	[24]
Ghana	80/118	48.8	47.5	80.5	[35,42]
Senegal	173	–	–	78.3	[35]
North Africa					
Egypt	120	28.8*	30.4	–	[43]
Morocco	64	55.5*	–	24.4*	[15,36]
Algeria	83	–	–	16.9*	[37]
Tunisia	102	–	–	10.8*	[36]
Libya	93	–	–	19.9*	[37]
Central Africa					
Cameroon	69	37	35	78	[26]
East Africa					
Tanzania	134/121	34	–	74	[29]
Ethiopia	264	31.4	–	–	[44]
South Africa					
South Africa	153	36	36	66	[26]
Zimbabwe	118	45	–	–	[27]

* statistically significant when compared to Malian.

alternative use of others antimalarials drugs. The frequency of CYP3A4 rs2740574 alleles observed in the Malian population (75%) was comparable to those reported in Ghana 80.5%,^[35] Senegal 78.3%,^[35] Cameroon 78%,^[26] Tanzania (74%),^[29] South Africa (66%),^[26] but significantly higher than those reported in North African Countries, including Morocco (24.4%),^[36] Algeria (16.9%),^[37] Tunisia (10.8%),^[36] and Libya (19.9%)^[37] (Table 2). The frequency of CYP3A4 rs2740574 is almost less than 5% in Europe and Asia, but more than 65% in populations of black African origin.^[32] The impact of CYP3A4 rs2740574 polymorphism on gene expression remains controversial when we review the data in the literature. However, some authors have reported that this SNP influences the metabolism of antimalarial drugs such as artemisinin combination and quinine.^[29,30] It has been reported that due to the reduced binding of a transcriptional repressor, the CYP3A4 rs2740574 variant leads to an increase in enzyme expression.^[38] However, a study in pregnant women from Tanzania reported that this variant was associated with decreased enzyme activity and that the clinical and parasitological therapeutic responses were comparable between homozygous wild-type and mutated carriers.^[39] Therefore, the identifying of the CYP3A4 rs2740574 variant in our patients with malaria could allow us to better understand the pharmacogenetic impact of this gene in the Malian population and to identify later those who are at high risk of toxicity. Besides infectious diseases, these SNPs have been documented in their susceptibility to certain chronic diseases such as neoplastic diseases. Zhou et al, in a meta-analysis, showed that carriers of the CYP3A4 rs2740574 variant in African populations are at increased risk of prostate cancer.^[40] Wang et al, in a meta-analysis showed that renal transplant recipients harboring CYP3A4 rs2740574 variant require a lower dose of cyclosporine compared to those carrying wild type alleles of CYP3A4.^[41] For this reason, the results of this study, which already provide an overview of this polymorphism in the Malian healthy population, will better guide the evidence-based prescription of this drug.

5. Conclusion

In the present study, we identified the genetic profiles of CYP2B6 rs3745274, CYP2B6 rs2279343 and CYP3A4 rs2740574 in a sample of the Malian population. The results obtained provide new insights on the distribution of drug metabolizing enzymes in the Malian population not described previously. In addition, they will contribute to the implementation of pharmacogenetic studies on drugs, which are substrates of these genes, in particular antiretrovirals and antimalarials for better genotype–phenotype correlation.

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References

- [1] Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance: a review. *Curr Drug Targets* 2017;19:38–54.
- [2] Pikuleva IA. Cytochrome P450s and cholesterol homeostasis. *Pharmacol Ther* 2006;112:761–73.
- [3] Durairaj P, Fan L, Du W, Ahmad S, Mebrahtu D, Sharma S, et al. Functional expression and activity screening of all human cytochrome P450 enzymes in fission yeast. *FEBS Lett* 2019;593:1372–80.
- [4] Xie F, Ding X, Zhang QY. An update on the role of intestinal cytochrome P450 enzymes in drug disposition. *Acta Pharm Sin B* 2016;6:374–83.
- [5] Purnapatre K, Khattar SK, Saini KS. Cytochrome P450s in the development of target-based anticancer drugs. *Cancer Lett* 2008;259:1–15.
- [6] Oostendorp RL, Marchetti S, Beijnen JH, Mazzanti R, Schellens JHM. The effect of hydroxyurea on P-glycoprotein/BCRP-mediated transport and CYP3A metabolism of imatinib mesylate. *Cancer Chemother Pharmacol* 2007;59:855–60.
- [7] Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin Pharmacokinet* 2005;44:879–94.
- [8] Van Erp NP, Gelderblom H, Karlsson MO, Li J, Zhao M, Ouwerkerk J, et al. Influence of CYP3A4 inhibition on the steady-state pharmacokinetics of imatinib. *Clin Cancer Res* 2007;13:7394–400.
- [9] Nelson DR. Gene nomenclature by default, or BLASTing to Babel. *Hum Genomics* 2005;2:196–201.
- [10] Lee YH. Assessing the causal association between smoking behavior and risk of gout using a Mendelian randomization study. *Clin Rheumatol* 2018;37:3099–105.
- [11] Ali GT, Al-azhary NM, Mokhtar DA. Frequency and prognostic significant of CYP3A4-A-290G polymorphism in acute myeloid leukemia. *J Adv Res* 2014;5:657–61.
- [12] Ding Y, Li Q, Feng Q, Xu D, Wu C, Zhao J, et al. CYP2B6 genetic polymorphisms influence chronic obstructive pulmonary disease susceptibility in the Hainan population. *Int J Chron Obstruct Pulmon Dis* 2019;14:2103–15.
- [13] Mukonzo JK, Nanzigu S, Waako P, Ogwal-Okeng J, Gustafson LL, Aklillu E. CYP2B6 genotype, but not rifampicin-based anti-TB cotreatments, explains variability in long-term efavirenz plasma exposure. *Pharmacogenomics* 2014;15:1423–35.
- [14] Ferreira PE, Veiga MI, Cavaco I, Martins JP, Andersson B, Mushin S, et al. Polymorphism of antimalaria drug metabolizing, nuclear receptor, and drug transport genes among malaria patients in Zanzibar, east Africa. *Ther Drug Monit* 2008;30:10–5.
- [15] Kassogue Y, Quachouh M, Dehbi H, Qessara A, Benchekroun S, Nadifi S. Functional polymorphism of CYP2B6 G15631T is associated with hematologic and cytogenetic response in chronic myeloid leukemia patients treated with imatinib. *Med Oncol* 2014;31:782–6.
- [16] Mikstacki A, Zakerska-Banaszak O, Skrzypczak-Zielinska M, Tamowicz B, Predecki M, Dorszewska J, et al. The effect of UGT1A9, CYP2B6 and CYP2C9 genes polymorphism on individual differences in propofol pharmacokinetics among Polish patients undergoing general anaesthesia. *J App Genet* 2017;58:213–20.
- [17] Miao J, Jin Y, Marunde RL, Kim S, Quinney S, Radovich M, et al. Association of genotypes of the CYP3A cluster with midazolam disposition in vivo. *Pharmacogenomics J* 2009;9:319–26.
- [18] Hoffman SMG, Nelson DR, Keeney DS. Organization, structure and evolution of the CYP2 gene cluster on human chromosome 19. *Pharmacogenetics* 2001;11:687–98.
- [19] Tornio A, Backman JT. Cytochrome P450 in pharmacogenetics: an update. 1st ed. *Adv Pharmacol* 2018.
- [20] Nyakutira C, Röshammar D, Chigutsa E, Chonzi P, Ashton M, Nhachi C, et al. High prevalence of the CYP2B6 rs3745274G→T* (6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol* 2008;64:357–65.
- [21] Penzak SR, Kabuye G, Mugenyi P, Mbamanya F, Natarajan V, Alfaro RM, et al. Cytochrome P450 2B6 (CYP2B6) Grs3745274T influences nevirapine plasma concentrations in HIV-infected patients in Uganda. *HIV Medicine* 2007;8:86–91.
- [22] Reay R, Dandara C, Viljoen M, Rheeders M. CYP2B6 haplotype predicts efavirenz plasma concentration in black South African HIV-1-infected children: a longitudinal pediatric pharmacogenomic study. *OMICS* 2017;21:465–73.
- [23] Shi WL, Tang HL, Zhai S. Di. Effects of the CYP3A4 δ 1B genetic polymorphism on the pharmacokinetics of tacrolimus in adult renal transplant recipients: a meta-analysis. *PLoS One* 2015;10:1–14.
- [24] McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. *Expert Opin Drug Metab Toxicol* 2012;8:371–82.
- [25] Solé X, Guinó E, Valls J, Iniesta R, Moreno V. SNPStats: a web tool for the analysis of association studies. *Bioinformatics* 2006;22:1928–9.
- [26] Swart M, Skelton M, Wonkam A, Kannemeyer L, Chin'ombe N, Dandara C. CYP1A2, CYP2A6, CYP2B6, CYP3A4 and CYP3A5 polymorphisms in two Bantu-speaking populations from Cameroon and South Africa: implications for global pharmacogenetics. *CPPM* 2012;10:43–53.
- [27] Rajeev KM, Mark NZ, Peter AZ. Prevalence of CYP2B6 alleles in malaria-endemic populations of West Africa and Papua New Guinea. *Eur J Clin Pharmacol* 2006;62:267–75.
- [28] Toyin A.S. ad , Olugbenga SJ, Ayodele BR, Joseph OO, Moji BOT. Allele and genotype frequencies of cytochrome P450 2B6 rs3745274G>T single nucleotide polymorphism in HIV-negative and HIV-infected adult Nigerian populations. *Am J Ther* 2016;23:e1715–9.
- [29] Hodel EMS, Csajka C, Ariey F, Guidi M, Kabanyanyi AM, Duong S, et al. Effect of single nucleotide polymorphisms in cytochrome P450 isoenzyme and N-acetyltransferase 2 genes on the metabolism of artemisinin-based combination therapies in malaria patients from Cambodia and Tanzania. *Antimicrob Agents Chemother* 2013;57:950–8.
- [30] Rodríguez-Antona C, Sayi JG, Gustafsson LL, Bertilsson L, Ingelman-Sundberg M. Phenotype-genotype variability in the human CYP3A locus as assessed by the probe drug quinine and analyses of variant CYP3A4 alleles. *Biochem Biophys Res Commun* 2005;338:299–305.
- [31] Ellison C, Abou El-Ella S, Tawfik M, Lein P, Olson J. Allele and genotype frequencies of CYP2B6 and CYP2C19 polymorphisms in Egyptian agricultural workers. *J Toxicol Environ Health A* 2012;75:232–41.
- [32] The International Genome Consortium. www.1000Genomes.org.
- [33] Ariyoshi N, Ohara M, Kaneko M, Afuso S, Kumamoto T, Nakamura H, et al. Q172H replacement overcomes effects on the metabolism of cyclophosphamide and efavirenz caused by CYP2B6 variant with Arg262. *Drug Metab Dispos* 2011;39:2045–8.
- [34] Marwa KJ, Schmidt T, Sjögren M, Minzi OMS, Kamugisha E, Swedberg G. Cytochrome P450 single nucleotide polymorphisms in an indigenous Tanzanian population: a concern about the metabolism of artemisinin-based combinations. *Malar J* 2014;13:1–7.
- [35] Zeigler-Johnson CM, Walker AH, Mancke B, Spangler E, Jalloh M, McBride S, et al. Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. *Human Hered* 2002;54:13–21.
- [36] Novillo A, Romero-Lorca A, Gaibar M, Bahri R, Harich N, Sánchez-Cuenca D, et al. Genetic diversity of CYP3A4 and CYP3A5 polymorphisms in North African populations from Morocco and Tunisia. *Int J Biol Markers* 2015;30:e148–51.
- [37] Fernández-Santander A, Novillo A, Gaibar M, et al. Cytochrome and sulfotransferase gene variation in north African populations. *Pharmacogenomics* 2016;17:1415–23.
- [38] Amirimani B, Ning B, Deitz AC, Weber BL, Kadlubar FF, Rebbeck TR. Increased transcriptional activity of the CYP3A4* 1B promoter variant. *Environ Mol Mutagenesis* 2003;42:299–305.
- [39] Mutagonda RF, Kamuhabwa AAR, Minzi OMS, Massawe SN, Asghar M, Homann MV, et al. Effect of pharmacogenetics on plasma lufenantrine pharmacokinetics and malaria treatment outcome in pregnant women. *Malar J* 2017;16:1–10.
- [40] Zhou LP, Yao F, Luan H, Wang YL, Dong XH, Zhou WW, et al. CYP3A4rs2740574 polymorphism and cancer risk: a HuGE review and meta-analysis. *Tumor Biol* 2013;34:649–60.
- [41] Wang C, Lu e, Chang KP, Guo Z, Qiao ML. Association of CYP3A4rs2740574 genotype with Cyclosporin A pharmacokinetics in renal transplant recipients: a meta-analysis. *Gene* 2018;664:44–9.
- [42] Klein K, Lang T, Saussele T, Barbosa-Sicard E, Schunck WH, Eichelbaum M, et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. *Pharmacogenet Genomics* 2005;15:861–73.
- [43] Ellison C, Abou El-Ella S, Tawfik M, Lein P, Olson J. CYP2C19 polymorphisms in Egyptian agricultural workers. *J Toxicol Environ Health A* 2012;75:232–41.
- [44] Ngaimisi E, Habtewold A, Minzi O, Makonnen E, Mugusi S, Amogne W, et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. *PLoS One* 2013;8.