Mol Biol Rep (2013) 40:3187–3192
DOI 10.1007/s11033-012-2393-2

Interethnic differences in *UGT1A4* genetic polymorphisms between Mexican Mestizo and Spanish populations

Marisol López · Pedro Dorado · Alberto Ortega · Eva Peñas-Lledó · Nancy Monroy · Irma Silva-Zolezzi · Jesús Cobaleda · Alicia Gallego-Aguilera · María Elisa Alonso · Adrián LLerena

Received: 24 September 2012 / Accepted: 17 December 2012 / Published online: 1 January 2013

Abstract UDP-glucuronosyltransferase 1A4 (UGT1A4) is a phase II drug-metabolizing enzyme that catalyzes the glucuronidation of many clinically-important drugs. Interethnic differences in the genetic polymorphism of *UGT1A4* have been reported; however, there is no information in Mexican Mestizos (MMs) and Spaniards (SPs). Furthermore, MM is an admixed population with 26 % of Caucasian genes mainly from Spain. Therefore, this study aimed to investigate the potential differences between 318 SPs and 248 MMs healthy individuals regarding *UGT1A4*1b*, *UGT1A4*2* and *UGT1A4*3* alleles and to compare the observed frequencies with those previously reported in different populations. The allelic frequencies of the three *UGT1A4* polymorphisms showed interethnic differences between MMs and SPs ($p < 0.05$). The analyzed SNPs variants in this genetic region were not in linkage disequilibrium (LD) for the MM population, suggesting that these mutations have arisen independently in the same genetic background. In contrast, *UGT1A4*2* and *UGT1A4*3* were in LD in the SP population. Comparison of present data with other in different ethnic groups revealed that the frequencies of *UGT1A4*2* and *UGT1A4*3* in SP were similar to other Caucasians and higher than in Asians, whereas in MMs were lower than in Caucasians and higher than in Asians only for *UGT1A4*2*. Present results could be helpful to improve the use of UGT1A4 drug substrates in order to adjust them to the ethnic background of a given population, specifically for Hispanics.

Keywords UGT1A4 · Glucuronidation · Interethnic differences · Mexican-Mestizo · Spaniards

Marisol López and Pedro Dorado contributed equally to this work.

M. López · A. Ortega
Department of Biological Systems, Universidad Autónoma Metropolitana-Xochimilco, Mexico City, Mexico

P. Dorado · E. Peñas-Lledó · J. Cobaleda · A. Gallego-Aguilera · A. LLerena (✉)
CICAB Centro de Investigación Clínica CIBERSAM, SES Servicio Extremeño de Salud, Hospital Universitario Infanta Cristina, 06080 Badajoz, Spain
e-mail: allerena@unex.es

N. Monroy · M. E. Alonso
Department of Neurogenetics and Molecular Biology, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico

I. Silva-Zolezzi
Department of BioAnalytical Sciences, Nestlé Research Center, Vers-chez-les-Blanc, Lausanne, Switzerland

J. Cobaleda
Centro de Salud Ciudad Jardín, SES Servicio Extremeño de Salud, Badajoz, Spain

Introduction

UDP-glucuronosyltransferases (UGTs) are considered among the most relevant phase II enzymes of drug metabolism. The reaction catalyzed by UGTs involves the addition of a glucuronic acid moiety to xenobiotics. Thus, UGT-mediated glucuronidation is a major path for the human body's elimination not only of about 35 % of all drugs metabolized by phase II enzymes, but also of foreign chemical removal for most drugs, dietary substances, toxins and endogenous substances [1–3].

The human UGT is a large gene superfamily, including the *UGT1A* locus on chromosome 2q37.1, which encodes at least nine functional proteins such as UGT1A4 [4].

UGT1A4 is known to be the primary enzyme that catalyzes *N*-glucuronidation mostly of primary, secondary and aromatic amines, including clinically-important drugs such as phenytoin, lamotrigine, olanzapine, tamoxifen, trifluoperazine, tacrolimus and amitriptyline [5–7]. In addition, UGT1A4 shows *O*-glucuronidation activity towards steroidal compounds and phytochemicals [8]. Nakajima et al. [9] have demonstrated that *UGT1A1* and *UGT1A4* polymorphisms might be a cause of the interindividual differences in *O*-glucuronidation of phenytoin in human liver microsomes. Ehmer et al. [10] identified the UGT1A4 P24T (c.70C>A) and L48V (c.142T>G) variants that exhibited reduced glucuronidation activities with substrate specificity. These natural variations of the *UGT1A4* gene show a differential hepatic metabolic activity toward mutagenic amines and endogenous steroids [10]. Recently, the variability of the clinical outcome in epileptic patients on monotherapy or polytherapy was found to be related to a decreased in the serum concentration of the antiepileptic drug, lamotrigine, due to the L48V polymorphism of *UGT1A4* [11]. In addition, data obtained in human liver microsomes suggest that the L48V polymorphism also contributes significantly to interindividual variability in olanzapine metabolism [12]. Zhou et al. [13] developed an in vitro evaluation with three recombinant UGT1A4 enzymes (UGT1A4 wild-type, UGT1A4 P24T and UGT1A4 L48V) demonstrating that the presence of these two last variants may lead to interindividual variations in lamotrigine metabolism in vivo.

The functional implications for the genetic polymorphisms in *UGT1A4* giving rise to the P24T and L48 V substitutions have been documented in several investigations [9–16]. In an association study, the L48 V change was studied in patients with schizophrenia suggesting that this SNP is associated with lower average plasma concentrations of olanzapine [12, 16]. Both, P24T and L48 V polymorphisms affect the UGT1A4 in vivo metabolism activity and may be good candidates for antiepileptic clinical response variation and as genetic causes of lamotrigine-induced adverse events [11, 16].

The synonymous *UGT1A4*1b* (C157C; c.471C>T) variant has been reported with a high frequency in Caucasians (20.9 % in French-Canadians and 15 % in Germans) [1, 10]. The C157C, P24T and L48V variants correspond to *UGT1A4*1b, *2* and **3* alleles, respectively [17].

The frequency of the genetic polymorphisms in *UGT1A4* has been reported for several populations revealing important differences among them [1, 10, 12, 17–23]; however there is no information regarding these polymorphisms in Mexican Mestizos (MM) and Spaniards (SP). Therefore, the main goal of this study was to determine the genotype and allele frequencies of *UGT1A4*1b, UGT1A4*2* and *UGT1A4*3* in a sample of MM and SP healthy volunteers.

Subjects and methods

Subjects

Participants were unrelated healthy volunteers of Mexican Mestizo ethnicity from Mexico City and surrounding areas (MMs; $n = 248$; 62 % female; age: 35 ± 16 years, range: 19–65 years) and of Caucasian Spaniard origin from Extremadura (SPs; $n = 318$; 51 % female; age: 43 ± 17 years, range: 18–70 years). The subjects were informed about the aims of the study and gave their written informed consent prior their participation. The study was performed according to the Helsinki Declaration and it was approved by the National Institute of Neurology and Neurosurgery (INNN) Internal Review Board (Mexico City, Mexico) and the Ethical Committee of the Extremadura University Hospital (Badajoz, Spain).

UGT1A4 genotyping

Genomic DNA was obtained from peripheral blood leukocytes by standard procedures. PCR–RFLP or real time PCR (RT–PCR) were employed to genotype the different allelic variants **1b, *2* and **3* of the gene *UGT1A4* (MIM 606429). Nomenclature of the three gene variations analyzed was according to the official page of UGT nomenclature [24] The SNPs 70C>A; P24T (rs6755571) and 471C>T; C157C (rs2011404) were genotyped with commercially available TaqMan validated SNP assays (C_25957120_10 and C_8739217_10) from Applied Biosystems (Applied Biosystems, Carlsbad, Massachusetts, USA). Amplification was done in accordance with manufacturer's instructions in an AB7300 real time PCR instrument. An allelic discrimination plot was used to identify individual genotypes (v2.0 software, Applied Biosystems). In order to scan the allelic variant 142T>G; L48V (rs2011425) (*1A4*3*), PCR–RFLP with the enzyme *Stu* I was performed with published primers [10, 16].

Subsequently, each allelic variant was confirmed by direct sequencing in five percent of the samples. Oligonucleotide primers and sequencing conditions were those published by Saeki et al. [15]. Purified amplicons were sequenced with Big Dye Terminator v3.1 Cycle Sequencing Kit and separated in a genetic analyzer AB3130 (Applied Biosystems, Carlsbad, Massachusetts, USA). All sequences were analyzed with Sequencing Analysis v5.3 and every allelic variant was confirmed by sequencing the product of an independent PCR on both strands and verified in different public databases. Nomenclature and positions of the diverse identified polymorphisms are relative to the adenine (+1) of the ATG of the reference sequence of NM_007120.2 → NP_009051.1.

Statistical analysis

The genotype and allele frequencies were assessed for Hardy–Weinberg equilibrium, differences in allele frequencies between the two studied populations and others were calculated by a Chi square test or Fisher′s exact test. A p value <0.05 was considered statistically significant. Statystical analyses were performed using GraphPad Prism 5.00 (GraphPad Software, Inc., San Diego; CA, USA). Linkage disequilibrium (LD) and haplotype analysis were performed using the Haploview software version 4.0 [25]. Haplotypes were inferred from individual genotypes using the software PHASE v2.1 [26]. Conditions employed for the haplotype inference procedure using 3 biallelic SNPs consisted in 100 iterations and 5 thinning interval steps through the Markov chain.

Results

The *UGT1A4* genotype frequencies corresponded to those predicted by the Hardy–Weinberg law. The most common genotypes in SPs and MMs were *wt/*1b* and *wt/*3*, respectively. Interestingly the genotype *UGT1A4*2/*2* was not identified in MMs and only in two SPs, being the least frequent genotype (Table 1). The allelic frequencies of *UGT1A4*2* and *UGT1A4*1b* (Table 2) were higher ($p < 0.05$) in SP individuals (6.9 % and 17.4 %) than in MMs (3.4 % and 7.6 %), respectively. In contrast, the allelic frequency of *UGT1A4*3* was higher ($p < 0.05$) in MMs than SPs. In Table 3, the allele frequencies found in this study are compared with those previously reported in other populations.

Haplotypes were inferred from the genotype data (Fig. 1). A total of seven and six different haplotypes were observed in MM and SP populations, respectively. However, the same four haplotypes above 5 % were observed in both populations but with different frequencies. In SPs, the most common haplotype was the wild-type (wt) CTC (68.0 %), and only three more haplotypes were found above 5 %: CTT (16.6 %), CGC (7.8 %) and ATC (6.5 %). The frequency of these haplotypes and the corresponding SNPs suggests that the C>T mutation in position 3 occurred first and the other two happened later and independently (Fig. 1a). In MMs, the most common haplotype was also the wt CTC (75.7 %), but only two other haplotypes were found above 5 %: CGC (12.8 %) and CTT (8.0 %) (Fig. 1b). The haplotype ATC (3.2 %) was the fourth most common but with a frequency <5 %. All these haplotypes correspond to those where the three SNPs are found independently in the same wild-type background.

Discussion

To our knowledge, this is the first study that examined the allele frequencies of *UGT1A4*1b, *2* and *3* in MM and SP individuals, showing significant differences in these three alleles between the two populations. Estimation of interethnic differences in relevant genetic polymorphisms is interesting for the clinical implementation of pharmacogenetics in order to optimize the drug treatments for a given population with regard to the ethnic background. This is one of the main goals to achieve by the Ibero-Latino-American network of Pharmacogenetics and Pharmacogenomics (RIBEF).

Table 1 Frequencies of *UGT1A4* genotypes among Mexican and Spanish healthy volunteers

Genotype	Mexican-Mestizo ($n = 248$)				Spaniards ($n = 318$)			
	n	Observed frequency	95 % IC	Expected frequency†	n	Observed frequency	95 % CI	Expected frequency†
wt/wt	144	0.581	0.5184–0.6404	0.575	149	0.470	0.4144–0.5234	0.449
*wt/*1b*	27	0.109	0.0755–0.1542	0.116	72	0.226	0.1837–0.2756	0.234
*wt/*2*	11	0.044	0.0241–0.0786	0.052	28	0.088	0.0612–0.1247	0.093
*wt/*3b*	50	0.202	0.1562–0.2561	0.199	28	0.088	0.0612–0.1247	0.116
*1b/*1b*	3	0.012	0.0024–0.0366	0.006	9	0.028	0.0142–0.0537	0.030
*1b/*2*	1	0.004	0.0001–0.0248	0.005	6	0.019	0.0077–0.0415	0.024
*1b/*3b*	4	0.016	0.0048–0.0422	0.020	15	0.047	0.0282–0.0770	0.030
*2/*2	0	0	0.0000–0.0184	0.001	2	0.006	0.0002–0.0242	0.005
*2/*3b	5	0.020	0.0073–0.0477	0.009	6	0.019	0.0077–0.0415	0.012
*3b/*3b	3	0.012	0.0024–0.0366	0.017	3	0.009	0.0019–0.0287	0.007

n number of subjects

† Calculated by Hardy–Weinberg law, (χ^2 test: MM $p = 0.3095$ and SP $p = 0.9527$)

Table 2 Frequencies of *UGT1A4* alleles among Mexican-Mestizo ($n = 248$) and Spanish ($n = 318$) healthy volunteers

UGT1A4	Mexican-Mestizo ($n = 248$)			Spaniards ($n = 318$)			
Alelles	*n*	Observed frequency	95 % IC	*n*	Observed frequency	95 % CI	*P* value[†]
wt	376	0.758	0.7184–0.7937	426	0.670	0.6292–0.7021	0.016
**1b*	38	0.076	0.0561–0.1036	111	0.174	0.1462–02051	0.0001
**2*	17	0.034	0.0211–0.0546	44	0.069	0.0515–0.0913	0.0113
**3b*	65	0.131	0.1040–0.1637	55	0.086	0.0707–0.1157	0.0193

N number of subjects, *MM* Mexican-Mestizos, *SP* Spaniards

[†] Fisher′s exact test, $\alpha = 0.05$

Table 3 *UGT1A4* allelic frequencies in the Mexican Mestizo and Spanish populations compared with other population studies

Population studied	*n*	Allelic frequency *UGT1A4*2*	MM *p* value[†]	SP *p* value[†]	Allelic frequency *UGT1A4*3b*	MM *p* value[†]	SP *p* value[†]	Reference
Caucasian	92	8.8	0.0045	0.3376	11.0	0.2530	0.3835	[19]
German	363	8.0	0.0010	0.4094	9.0	0.0302	0.8487	[10]
French-Canadian	254	4.9	0.2712	0.1707	8.3	0.0141	0.8318	[1]
Asian	46	0.0	0.0891	0.0388	19.6	0.1051	0.0026	[19]
Japanese	256	0.0	0.0001	0.0001	12.9	0.8515	0.0206	[15]
Japanese	301	0.0	0.0001	0.0001	13.0	1.0000	0.0168	[20]
Japanese	100	0.0	0.0049	0.0001	16.5	0.2782	0.0023	[18]
Korean	50	0.0	0.0913	0.0023	12.0	0.8708	0.4740	[21]
Jordanian	216	6.5	0.0327	0.8050	3.5	0.0010	0.0003	[22]
African	59	0.0	0.0541	0.0009	9.0	0.3500	0.8590	[23]
Spaniard	318	6.9	0.0113		8.6	0.0193		This study
Mexican-Mestizo	248	3.4			13.1			

n number of subjects, *MM* Mexican-Mestizos, *SP* Spaniards

[†] Fisher′s exact test, $\alpha = 0.05$

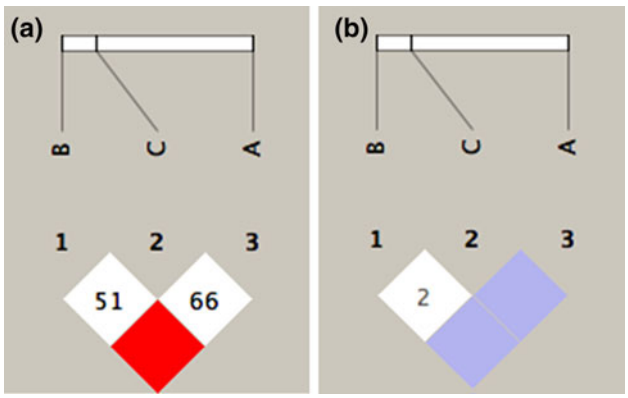

Fig. 1 Haplotype structure of *UGT1A4* allelic variants studied produced by Haploview software. (**a**) Spanish population; (**b**) Mexican population. (B = *UGT1A4**2; C = *UGT1A4**3b; A = *UGT1A4**1b), relative distances B–C = 72 nt, C–A = 392 nt, B–A = 401 nt. (nt = nucleotide). D′ values 0–1 are shown. White boxes: D′ < 1 and LOD < 2; blue boxes: D′ = 1 and LOD < 2; red boxes: D′ = 1 and LOD > 2. LOD = log odds score for linkage disequilibrium. D′ = 1 indicates that the two SNPs have not been separated by recombination. LOD > 2 indicates strong evidence of LD. Lower D′ values indicate some evidence of recombination

The synonymous C157C variant (*UGT1A4*1b*) was included in the present study because it showed high heterozygosis in an initial pre-screening. The *UGT1A4*1b* allele frequencies were different between MMs and SPs (Table 2). This is in agreement with the 1000 Genomes Project data, where a higher allele frequency of *UGT1A4*1b* was observed for Europeans (18 %) *vs.* admixed Americans (13 %). Indeed, this allele is very rare in Asian (1 %) and African (4 %) populations [23].

*UGT1A4*2* frequency was two times higher in SPs than in MMs. In contrast, *UGT1A4*3* was lower in SPs than in MMs. These allele frequencies also presented interethnic differences with other published populations (Table 3). *UGT1A4*2* and *UGT1A4*3* frequencies *in SPs* were similar to those reported in other Caucasian populations [1, 10, 19]. However, in MMs, the frequency of *UGT1A4*2* was lower and *UGT1A4*3* was higher than in several Caucasian populations. The frequencies of *UGT1A4*2* in SPs and MMs were higher than those observed in Asian populations [15, 18, 21], whereas the *UGT1A4*3* frequencies were lower in SPs but similar in MMs compared to Asians. In addition, the allele frequency of

*UGT1A4*2* in Jordanians was similar in SPs but higher than in MMs, while *UGT1A4*3* in Jordanians was two and three times lower than in SPs and MMs, respectively [22]. In Africans *UGT1A4*2* is absent [23], being higher in both SPs and MMs, whereas *UGT1A4*3* frequency was similar to both SPs and MMs observed frequencies.

In general, contrary to the relative homogeneity observed in SPs within Caucasians for *UGT1A4**2 and *UGT1A4*3*, MMs exhibited differences when compared to Caucasians [10, 19]. While the *UGT1A4**2 frequencies were found to be similar in SPs and Jordanians, *UGT1A4*3* frequencies were similar among SPs, MMs and Africans and between MMs and Asians. Thus, the distribution of *UGT1A4*2* and *UGT1A4*3* in the MM population might be influenced by its admixture characteristics. Genetic admixture and diversity estimations in MM have been characterized, revealing a 69 % of Amerindian, 26 % of European, which comes mainly from Spain (Castilla, Andalucía, and Extremadura), and 5 % of African contribution [27].

The three analyzed SNPs variants in this genetic region indicated positive LD for *UGT1A4*2* and *UGT1A4*3* for the SP population. However, these variants are not in LD in the MM population, suggesting that these mutations have arisen independently in the same genetic background.

The substitutions P24T and L48 V have been observed to be in LD in Germans, but not in the French-Canadian population [10, 17]. The LD pattern observed in the French-Canadian population was similar to that in the MM. In contrast, Haploview analysis indicated positive LD between *UGT1A4*2* and *UGT1A4*3* variants for the SP population, in a manner similar to Germans. These allelic variants have been associated with reduced glucuronidation activities [10]. The discrepancies in LD pattern between SPs and MMs could be attributed to ethnic differences and additional studies must clarify whether this non-random association of these alleles may contribute to differences in the glucuronidation of UGT1A4.

Present data confirm that the three analyzed *UGT1A4* variants are highly polymorphic in the studied MM and SP populations. Functional variants of UGT1A4 have been shown to exhibit differences in glucuronidation capacity that may contribute significantly to interindividual variability in drug metabolism [11, 16]. Taking into account that UGT1A4 metabolizes many therapeutic drugs widely used in SPs and MMs, it is plausible to suggest that the observed genetic differences in both populations might partially explain differences in drug responses among them. In the light of these findings, we could hypothesize that drugs metabolized by UGT1A4 may show different profile of efficacy/adverse effects in MM and SP populations. Therefore, further research on different ethnic groups in America is warranted.

Acknowledgments The study has been partly supported by the Institute of Health Carlos III-FIS and the European Union (FEDER) Grants PI10/02758, PI10/02010 and CP06/00030 (P. Dorado) and from PRIS Extremadura, Consejería de Sanidad y Dependencia, FundeSalud PRIS10043 and PRIS11051 Gobierno de Extremadura AEXCID Cooperacion Extremeña (11IA002); by a Grant from Consejo Nacional de Ciencia y Tecnología de Mexico (CONACYT #167261) and was coordinated in the SIFF-RIBEF network (Red Iberoamericana de Farmacogenética y Farmacogenomica; www.ribef.com). The technical assistance of Esther Machín, Inés López and Beatriz Grillo is gratefully acknowledged.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ménard V, Girard H, Harvey M, Pérusse L, Guillemette C (2009) Analysis of inherited genetic variations at the UGT1 locus in the French-Canadian population. Hum Mutat 30:677–687
2. Bock KW (2010) Functions and transcriptional regulation of adult human hepatic UDP-glucuronosyl-transferases (UGTs): mechanisms responsible for interindividual variation of UGT levels. Biochem Pharmacol 80:771–777
3. Hahn KK, Wolff JJ, Kolesar JM (2006) Pharmacogenetics and irinotecan therapy. Am J Health Syst Pharm 63:2211–2217
4. Zhang W, Liu W, Innocenti F, Ratain MJ (2007) Searching for tissue-specific expression pattern-linked nucleotides of UGT1A isoforms. PLoS ONE 2:e396
5. Laverdière I, Caron P, Harvey M, Lévesque E, Guillemette C (2011) In vitro investigation of human UDP-glucuronosyltransferase isoforms responsible for tacrolimus glucuronidation: predominant contribution of UGT1A4. Drug Metab Dispos 39:1127–1130
6. López M, Dorado P, Monroy N, Alonso ME, Jung-Cook H, Machín E, Peñas-Lledó E, Llerena A (2011) Pharmacogenetics of the antiepileptic drugs phenytoin and lamotrigine. Drug Metab Drug Interact 26:5–12
7. Kaivosaari S, Finel M, Koskinen M (2011) *N*-glucuronidation of drugs and other xenobiotics by human and animal UDP-glucuronosyltransferases. Xenobiotica 41:652–669
8. Mohamed ME, Frye RF (2011) Inhibitory effects of commonly used herbal extracts on UGT1A4, 1A6, and 1A9 enzyme activities. Drug Metab Dispos 39:1522–1528
9. Nakajima M, Sakata N, Ohashi N, Kume T, Yokoi T (2002) Involvement of multiple UDP-glucuronosyltransferase 1A isoforms in glucuronidation of 5-(4′-hydroxyphenyl)-5-phenylhydantoin in human liver microsomes. Drug Metab Dispos 30:1250–1256
10. Ehmer U, Vogel A, Schütte JK, Krone B, Manns MP, Strassburg CP (2004) Variation of hepatic glucuronidation: novel functional polymorphisms of the UDP-glucuronosyltransferase UGT1A4. Hepatology 39:970–977
11. Gulcebi MI, Ozkaynakcı A, Goren MZ, Aker RG, Ozkara C, Onat FY (2011) The relationship between UGT1A4 polymorphism and serum concentration of lamotrigine in patients with epilepsy. Epilepsy Res 95:1–8
12. Erickson-Ridout KK, Zhu J, Lazarus P (2011) Olanzapine metabolism and the significance of UGT1A448V and UGT2B1067Y variants. Pharmacogenet Genomics 21:539–551
13. Zhou J, Argikar UA, Remmel RP (2011) Functional analysis of UGT1A4 (P24T) and UGT1A4 (L48 V) variant enzymes. Pharmacogenomics 12:1671–1679

14. Wiener D, Doerge DR, Fang JL, Upadhyaya P, Lazarus P (2004) Characterization of *N*-glucuronidation of the lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human liver: importance of UDP-glucuronosyltransferase 1A4. Drug Metab Dispos 32:72–79
15. Saeki M, Saito Y, Jinno H et al (2005) Genetic variations and haplotypes of UGT1A4 in a Japanese population. Drug Metab Pharmacokinet 20:144–151
16. Ghotbi R, Mannheimer B, Aklillu E et al (2010) Carriers of the UGT1A4 142T>G gene variant are predisposed to reduced olanzapine exposure an impact similar to male gender or smoking in schizophrenic patients. Eur J Clin Pharmacol 66:465–474
17. Benoit-Biancamano MO, Adam JP, Bernard O, Court MH, Leblanc MH, Caron P, Guillemette C (2009) A pharmacogenetics study of the human glucuronosyltransferase UGT1A4. Pharmacogenet Genomics 19:945–954
18. Mori A, Maruo Y, Iwai M, Sato H, Takeuchi Y (2005) UDP-glucuronosyltransferase 1A4 polymorphisms in a Japanese population and kinetics of clozapine glucuronidation. Drug Metab Dispos 33:672–675
19. Thomas SS, Li SS, Lampe JW, Potter JD, Bigler J (2006) Genetic variability, haplotypes, and htSNPs for exons 1 at the human UGT1A locus. Hum Mut 27:717
20. Saeki M, Saito Y, Jinno H et al (2006) Haplotype structures of the UGT1A gene complex in a Japanese population. Pharmacogenomics J 6:63–75
21. Yea SS, Lee SS, Kim WY, Liu KH, Kim H et al (2008) Genetic variations and haplotypes of UDP-glucuronosyltransferase 1A locus in a Korean population. Ther Drug Monit 30:23–34
22. Hakooz N, Alzubiedi S, Yousef AM, Arafat T, Dajani R, Ababneh N, Ismail S (2012) UDP-glucuronosyltransferase 1A4 (UGT1A4) polymorphisms in a Jordanian population. Mol Biol Rep 39:7763–7768
23. 1000 Genomes Project. http://www.1000genomes.org/
24. http://www.pharmacogenomics.pha.ulaval.ca/webdav/site/pharmacogenomics/shared/Nomenclature/UGT1A/UGT1A4.htm
25. Haploview v4.0 software. http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview
26. Phase v2.1 software. http://www.stat.washington.edu/stephens/phase/download.html
27. Juárez-Cedillo T, Zúñiga J, Acuña-Alonzo V, Pérez-Hernández N, Rodríguez-Pérez JM et al (2008) Genetic admixture and diversity estimations in the Mexican-Mestizo population from Mexico City using 15 STR polymorphic markers. Forensic Sci Int Genet 2:e37–e39