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Differences in frequencies of UGT1A9, 1A7, and 1A1 genetic polymorphisms in Chinese Tibetan versus Han Chinese populations

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ABSTRACT. As part of a series of pharmacogenomics studies of the Chinese population, we investigated genetic polymorphisms of some UGT1A regions. The three genes that were analyzed were UGT1A9, 1A7, and 1A1; we sequenced their exons, together with promoters, surrounding introns and 3'-untranslated regions (3'UTR) in 100 unrelated-healthy Chinese Tibetan individuals. We compared the data with information on Han Chinese of the same region, which we downloaded from the HapMap database. We identified 40 polymorphisms; 16 of them were shared by the two populations. We then analyzed their linkage disequilibrium map. The UGT1As cluster can be divided into two linkage blocks in the Tibetan population: Block 1 (UGT1A9, UGT1A7), Block 2 (3'-UTR). Furthermore, we identified haplotypes and selected their tagSNPs. In exon 1 of UGT1A7 gene, 393G>A (Arg131Gln, rs17868324) was found at a frequency of 44.4% in the Tibetan population, compared to only 0.7% in the Han population. The linkage blocks in the Han Chinese sample differed from that of the Chinese Tibetan group; the former had Block 1 (UGT1A9,

UGT1A7), Block 2 (UGT1A7), and Block 3 (3'-UTR). These findings provide fundamental information for future molecular genetic studies of the UGT1A gene cluster as well as for personalized medicine in Chinese.

Key words: *UGT1A*; Tibetan; Chinese Han in Beijing, China (CHB); Linkage disequilibrium; Haplotype

INTRODUCTION

Glucuronidation, mediated by the UDP-glucuronosyltransferases (UGTs), is one of the critical steps in the detoxification and elimination of various endogenous and exogenous compounds (Tukey and Strassburg, 2000; Miners et al., 2002). This reaction, which adds a UDP-glucuronic acid moiety to xenobiotics for the formation of inactive glucuronides, can account for ~35% of all phase II drug metabolites (Evans and Relling, 1999). Consistent with its broad substrate profile, the UGT complex produces a number of isoforms by alternative splicing, as a superfamily of independently regulated enzymes (Gong et al., 2001). The N-terminal domain encoded by each exon 1 of *UGT1A* determines the substrate-binding specificity, and the C-terminal domain encoded by exons 2-5 is of importance for binding to the common cofactor, UDP-glucuronic acid (Radominska-Pandya et al., 1999). The human *UGT1A* gene complex, spans approximately 200 kb on chromosome 2q37, and consists of nine active and four inactive exon 1 segments (in the following segment order: *UGT1A12P*, *1A11P*, *1A8*, *1A10*, *1A13P*, *1A9*, *1A7*, *1A6*, *1A5*, *1A4*, *1A3*, *1A2P*, and *1A1*) and common exons 2-5 (Gong et al., 2001; Bock, 2003).

Genetic polymorphisms of *UGT1As* have important clinical implications (Raijmakers et al., 2000; Fisher et al., 2000). Some of these polymorphisms are highly relevant as they exert a significant effect on UGT1A enzymatic function (Iyer et al., 2002; Guillemette, 2003). Some are also associated with Crigler-Najjar syndrome, in which the enzyme's activity is either less than 10% of normal or completely absent (Evans and Relling, 1999; Verlaan et al., 2004). Genetic polymorphisms, including single nucleotide polymorphisms (SNPs), can account for much of this enormous variation (Ando et al., 2000; Burchell, 2003). In the promoter, a TATA box variant -52$(TA)_7$, implicated in Gilbert syndrome in Caucasians, reduces glucuronidation of bilirubin in hepatic tissue (Bosma et al., 1995; Beutler et al., 1998) and has been associated with an increased risk of breast cancer (Guillemette et al., 2000; Tsezou et al., 2007). *In vitro* studies have highlighted that one thymidine base deletion at position -118 of the *UGT1A9* gene [-118$(T)_{9/10}$] is associated with reduced gene expression (Korprasertthaworn et al., 2009). In addition, some polymorphisms have also been linked to increased risk for hepatocellular carcinoma (Wang et al., 2004) and orolaryngeal cancer (Zheng et al., 2001).

In addition, genetic polymorphisms of *UGT1A9*, *1A7*, and *1A1* have been previously studied in different ethnic populations and found to exhibit remarkable interethnic difference in distribution and frequency spectrum. Meanwhile, rather than individual SNPs, haplotypes, linked combinations of SNPs on a chromosome, can accurately investigate the associations between genotypes and phenotypes (Clark, 2004; Kitsios and Zintzaras, 2009). Therefore, for one selected ethnic group, we should combine more than one gene to analyze the specific distribution of genetic polymorphisms and their important roles in optimizing therapeutic efficiency (Maitland et al., 2006; Zintzaras and Lau, 2008). Although genetic polymorphisms of *UGT1A* genes have been studied, most research has focused on the effects of *UGT1A1*28* and *UGT1A1*6* variations. A comprehensive analysis for genetic polymorphisms of *UGT1A9*, *1A7*, and *1A1* genes in Tibetan

healthy subjects has rarely been conducted. Regardless of factors such as gender and exposure to environmental inducers (Ritter et al., 1999), the key aspect to explain the variability of enzymatic activity is the polymorphisms of *UGT1As* within genetic subgroups.

However, there has been no previous haplotype analysis with a high SNP density for the complex of the *UGT1A9*, *1A7*, and *1A1* genes between the Chinese Tibetan population and Han sample. In this study, we screened the genetic polymorphisms for all their exons together with promoters, surrounding introns and 3'UTR and inferred the haplotype structures of the complex region for these two groups.

MATERIAL AND METHODS

Subjects

Peripheral blood samples were obtained from 100 unrelated healthy Chinese individuals after their use in routine physical examinations. The study subjects consisted of 100 Tibetan individuals (50 males and 50 females) from Qinghai, aged between 18 and 40 years. To ensure their Tibetan Chinese origin, they were interviewed regarding their ancestral status for up to three previous generations. The standard informed consent was provided by the volunteers before participating in the study. The project was reviewed and approved by the Ethical Committee of Northwest University, Shaanxi, China.

Genotyping and HapMap analysis

Genomic DNA was isolated from peripheral blood leukocytes using a standard procedure (Okuda et al., 2002). Three *UGT1A* first exons, five common exons, and their surrounding regions were sequenced in 100 healthy Chinese subjects and analyzed on the ABI PRISM 3700 DNA analyzer (Applied Biosystems, Foster City, CA, USA). Sequences alignments were carried out with the Sequencher 4.10.1 software (Gene Codes Corporation, Ann Arbor, MI, USA). The gene-specific primer pairs were designed according to the reference sequence AF297093.1 (Zhang et al., 2012). We downloaded the genotyping data on the Chinese Han in Beijing, China (CHB, 139 unrelated individuals) from the HapMap database (http://hapmap.ncbi.nlm.nih.gov), and made comparisons with our data on the Chinese Tibetan in Qinghai.

Haplotype analysis and tag SNP selection

According to the confidence-interval method (Gabriel et al., 2002), we obtained the whole structure of *UGT1A9*, *IA7*, and *1A1* genetic polymorphisms using the Haploview 4.2 software (Massachusetts Institute of Technology, Cambridge, MA, USA). We compared the information of haplotype structure, linkage disequilibrium (LD) and the potential haplotype tag SNPs (htSNP) in each LD block among Chinese Han from the HapMap database with our data on the Chinese Tibetan.

RESULTS

Polymorphism comparisons of UGT1A9, 1A7, and 1A1 genes in two populations

A total of 36 different genetic polymorphisms were detected in the sequenced regions of

UGT1A9, *1A7*, and *1A1* genes in the 100 Chinese Tibetan subjects. To compare with the Chinese Han cohort, we downloaded the genotypes, allele frequencies and genotype frequencies of the CHB groups from the HapMap Database. We found that 16 polymorphisms are shared with CHB, of which 1 polymorphism (6634C>T, rs6708136) was checked showing no minor allele frequency (MAF) in CHB, while it showed a low frequency of 0.005 for the T allele in the Tibetan population. It exists in *UGT1A* common intron 1 (Table 1). In the *UGT1A9* promoter region, four special polymorphisms, namely -1218G>A (rs17864684), -1213G>A (rs2741044), -1107G>A (rs28970010) and -87G>A (rs17868322), existed only in the CHB samples with frequencies <10%. For the Tibetan population, there were also some special polymorphisms found in our study: -2189T>C, -1819T>C, -118delT and 588G>T of *UGT1A9*; -561A>C, -543A>G, -103G>C, -129insC, 387T>G, 391C>A, 622T>C and 660C>T of *UGT1A7*; -53(TA)6/7, 181G>A and 596C>G of *UGT1A1*; and 6634C>T, 6637A>C, 7939C>T, 8046A>C, 12022C>T and 12691T>C in the common region of *UGT1As*.

Table 1. Polymorphisms and frequencies of UGT1As detected in Tibetan and Chinese Han (CHB) populations.

	Nucleotide change	Amino acid change	MAF		
			Tibetan (N = 200)	CHB (N = 278)	
1A9 Promoter	-2189T>C		0.005	0	Novel
	-1888T>G		0.11	0.051	rs6731242
	-1819T>C		0.36	0	rs13418420
	-1218G>A		0	0.093	rs17864684
	-1213G>A		0	0.011	rs2741044
	-1107G>A		0	0.067	rs28970010
	-441C>T		0.035	0.026	rs2741045
	-332T>C		0.045	0.011	rs2741046
	-118delT		0.449	0	rs67695772
	-87G>A		0	0.007	rs17868322
1A9 Exon1	588G>T	Gly196Gly	0.02	0	novel
1A7 Promoter	-561A>C		0.022	0	novel
	-543A>G		0.245	0	rs4530361
	-341C>T		0.126	0.133	rs28946877
	-103G>C		0.005	0	novel
	-57T>G		0.298	0.248	rs7586110
1A7 Exon1	33C>A	Pro11Pro	0.291	0.233	rs7577677
	-129insC	Frameshift	0.005	0	novel
	387T>G	Asn129Lys	0.444	0	rs17868323
	391C>A	Arg131Arg	0.449	0	rs17863778
	392G>A	Arg131Gln	0.444	0.007	rs17868324
	622T>C	Trp208Arg	0.298	0	rs11692021
	660C>T	Cys220Cys	0.005	0	rs45462096
	756G>A	Leu252Leu	0.136	0.133	rs17864686
1A1 Promoter	-364C>T		0.135	0.128	rs887829
	-64G>C		0.082	0.036	rs873478
	-53(TA)6/7		0.130	0	rs3064744
1A1 Exon 1	181G>A	Ala61Thr	0.03	0	novel
	211G>A	Gly71Arg	0.2	0.208	rs4148323
	596C>G	Ser199Cys	0.01	0	novel
1A Intron 1	6634C>T		0.005	0	rs6708136
	6637A>C		0.005	0	novel
1A Intron 2	6893T>C		0.095	0.022	rs4148327
1A Exon 4	7939C>T	Pro364Leu	0.085	0	rs34946978
	8046A>C	Asn400His	0.01	0	rs111033540
1A Exon 5	12022C>T	Pro451Leu	0.02	0	rs114982090
1A 3'UTR	12483T>C		0.15	0.124	rs10929303
	12611G>C		0.135	0.156	rs1042640
	12691T>C		0.01	0	rs34942353
	12712G>C		0.13	0.156	rs8330

UTR = untranslated region. MAF = minor allele frequency. The A of the ATG of the initiator Met codon is nucleotide +1, according to the reference sequence NT_005120.16 in GenBank. The P-value is the test of difference in minor allele frequencies between the two ethnic groups.

The common SNPs of the *UGT1A9*, *1A7*, and *1A1* genes in the Chinese Tibetan and CHB samples showed ethnic-specific frequencies. For example, *UGT1A7* rs17868324 (392G>A) displayed a frequency of 0.444 in the Chinese Tibetan population, but was very rare (0.007) in CHB. Comparing the two populations, many SNPs had similar frequencies in these two populations, for example: -1888T>G (rs6731242) and -441C>T (rs2741045) of *UGT1A9*; -341C>T (rs28946877), -57T>G (rs7586110), 33C>A (rs7577677) and 756G>A (rs17864686) of *UGT1A7*; -364C>T (*1A1*80*, rs887829), 211G>A (*1A1*6*, rs4148323) and -64G>C (*1A1*81*, rs873478) of *UGT1A1* (Table 2); and the 3'UTR SNPs 12483T>C, 12611G>C and 12712G>C. In our study, we found four common identified alleles of *UGT1A7*11*, *UGT1A1*6*, *UGT1A1*80* and *UGT1A1*81* shared by the Tibetan population and CHB sample. They all showed similar frequencies in the two populations (Table 2).

Table 2. Allele frequencies of UGT1As polymorphisms in Tibetan and CHB populations.

Ethnicity	Numbers	UGT1A7		UGT1A1	
		*11	*6	*80	*81
Tibetan	200	0.01	0.200	0.135	0.082
CHB	278	0.007	0.208	0.128	0.036

The allele was based on the criteria posted on the UGT alleles Nomenclature home page (http://galien.pha.ulaval.ca/labocg/alleles/alleles.html).

Comparison of LD map in two populations

For close comparison, we used the common polymorphisms in two populations to analyze the LD maps for the *UGT1A9*, *1A7*, and *1A1* genes. We performed an LD analysis using 15 common polymorphisms of the Tibetan and CHB datasets. These two populations had highly similar LD maps (Figure 1). For example, both populations had one similar LD block of 12483T>C (rs10929303), 12611G>C (rs1042640), and 12712G>C (rs8330). However, -57T>G and 33C>A comprised another block in the *UGT1A7* gene for the CHB population, but not in the Tibetan population. Moreover, we also found some strong LD for polymorphisms between different genes. For example, -1888T>G in promoter of *UGT1A9* gene showed a high LD with -341C>T and 756G>A of *UGT1A7* gene, together with -64G>C in the promoter of *UGT1A1* gene for Tibetan population ($r^2 > 0.5$). This was obviously different from the CHB population ($r^2 < 0.3$). In the Tibetan population, -341C>T in the promoter of the *UGT1A7* gene showed a high LD with -64G>C in the promoter of the *UGT1A1* gene ($r^2 = 0.5$), while only $r^2 = 0.07$ in the CHB sample.

Haplotype comparisons in two populations

To compare the whole structure of the *UGT1A9*, *1A7*, and *1A1* polymorphisms, we performed a haplotype analysis of all SNPs in our study for the two populations respectively. We listed the haplotypes with a frequency >5% (Table 3). We observed that one common LD block and two common haplotypes of *UGT1As* were shared by these two populations. The common LD blocks were consisted of three same markers 12483T>C, 12611G>C, and 12712G>C, while the haplotype tag SNPs were different. 12611G>C was within the CCC haplotype in Tibetan population but not in CHB. All common haplotypes shared between Tibetan and CHB showed similar frequencies.

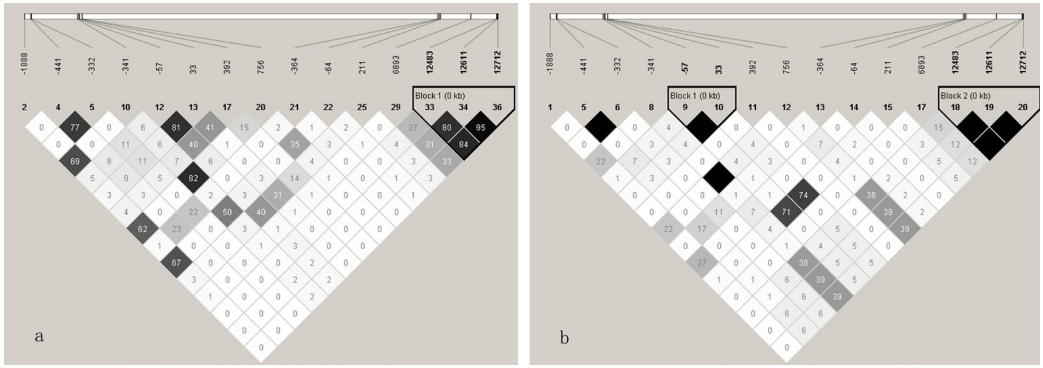

Figure 1. Pairwise linkage disequilibrium of *UGT1A9, 1A7*, and *1A1* genes in Chinese Tibetan (**a**) and CHB (**b**) populations. An r^2 color scheme is used to display LD with black for very strong LD ($r^2 = 1$), white for no LD ($r^2 = 0$), and shades of intermediate LD ($0 < r^2 < 1$). The data in the square indicate the r^2 value according to Gabriel's definition.

Table 3. Haplotype analysis of each LD block in Tibetan and CHB populations.

Population	Block	Markers	Haplotype	Population frequencies	htSNPs
Tibetan (N = 100)	1	-543A>G, -341C>T, -57T>G, 33C>A, 387T>G, 391C>A	ACTCTC	0.529	-543A>G, -341C>T, -57 T>G, 33C>A, 387T>G
			GCGAGA	0.214	
			ATTCGA	0.119	
			ACGAGA	0.054	
	2	12483T>C, 12611G>C, 12712G>C	CCC	0.845	12483T>C, 12611G>C
			TGG	0.130	
CHB (N = 139)	1	-1218G>A, -1107G>A, -341C>T	GGC	0.867	-1218G>A, -1107G>A, -341C>T
			AAT	0.067	
	2	-57T>G, 33C>A	TC	0.748	-57 T>G
			GA	0.252	
	3	12483T>C, 12611G>C, 12712G>C	CCC	0.876	12483T>C
			TGG	0.124	

htSNPs are haplotype tag SNPs.

We noted that there was ethnic specificity in the haplotype distribution of these two populations. For example, the Tibetan population showed one haplotype, ACTCTC, with a frequency of 52.9% for the specific LD block of -543A>G, -341C>T, -57T>G, 33C>A, 387T>G and 391C>A. Moreover, CHB had two different LD blocks: Block 1 of -1218G>A, -1107G>A and -341C>T (haplotype GGC with a frequency of 86.7%) and Block 2 of -57T>G and 33C>A (haplotype TC with a frequency of 74.8%).

DISCUSSION

We further compared polymorphism frequencies of the *UGT1A9*, *1A7* and *1A1* genes between different ethnic groups and demonstrated a remarkable interpopulation difference. In our Chinese Tibetan population, *UGT1A9*1b* (-118delT) remained the most common variant, which is in agreement with previous investigation in Asian population (Yamanaka et al., 2004). rs67695772 is located in the promoter of the *UGT1A9* genes. Its frequency in the Chinese Tibetan population was 44.9%, and a higher level of 61% was reported in the Korean

population. For 211G>A, Caucasians did not display this polymorphism in 92 samples as reported in the Asian population (Thomas et al., 2006). It showed similar frequencies of ~20% in our Chinese Tibetan and CHB groups as reported in the Korean population (Yea et al., 2008). Some *UGT1A* SNPs have been reported to be associated with diseases such as Crigler-Najjar syndrome. Therefore, these *UGT1A* SNPs may be used as biomarkers for assessing individualized disease risk, even for personalized medical therapy. Meanwhile, owing to the differential linkage disequilibrium between SNPs, haplotypes have greater power to be used for genotype-phenotype study. It is necessary to analyze the haplotypes of the *UGT1A* locus in a larger population sample.

To assist in pharmacogenomic studies in Chinese, we comprehensively investigated the genetic polymorphisms of *UGT1A9*, *1A7*, and *1A1* genes in a Chinese population. We sequenced all their exons together with promoters, surrounding introns and 3' untranslated regions (3'UTR) from 100 unrelated healthy Chinese Tibetan individuals. In comparing the findings with Chinese Han information (CHB from the HapMap database), we identified 40 polymorphisms, of which 16 were shared by these two populations. We then analyzed their linkage disequilibrium (LD) map. The *UGT1As* cluster could be divided into two linkage blocks in the Tibetan population: Block 1 (*UGT1A9*, *UGT1A7*), Block 2 (3'UTR). Furthermore, we identified the haplotypes and selected their tag SNPs. Finally, a comparison of our data with CHB samples of the HapMap project revealed the ethnic specificity of the *UGT1A* genetic diversity in Chinese. Meanwhile, we found three linkage blocks in the CHB sample, which was very different from the Chinese Tibetan group. These findings provide essential information for future molecular genetic studies of the *UGT1A* gene cluster as well as for personalized medicine in Chinese.

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