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• *BASIC RESEARCH* •

Polymorphisms of uridine-diphosphoglucuronosyltransferase 1A7 gene in Taiwan Chinese

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Abstract

AIM: Single nucleotide polymorphisms (SNPs) of uridine-diphosphoglucuro-nosyltransferase 1A7 (UGT1A7) gene are associated with the development of orolaryngeal cancer, hepatocellular carcinoma, and colorectal cancer. We performed this research to establish the techniques for determining UGT1A7 gene and basic data of this gene for Taiwan Chinese.

METHODS: We collected blood samples from 112 healthy adults and 505 subjects carrying different genotypes of UGT1A1, and determined the promoter area and the entire sequence of UGT1A7 exon 1 by polymerase chain reaction. We designed appropriate primers and restriction enzymes to detect variant UGT1A7 genotypes found in the study subjects.

RESULTS: Six SNPs at nucleotides 33, 387, 391, 392, 622, and 756 within the coding region of UGT1A7 exon 1 were found. The incidence of UGT1A7 *1/*2 (N129R131W208/K129K131W208) was predominant (35.7%) while that of UGT1A7 *3/*3 (K129K131R208/K129K131R208) was the least (2.7%). The allele frequency of UGT1A7*3, which exists in a considerable proportion of Caucasians (0.361) and Japanese (0.255), was identified only to be 0.152 in our study subjects. A novel variation at nucleotide -57 in the upstream was found, which was associated with SNPs at nucleotides 33, 387, 391, 392, and 622 in one of the variant haplotypes. The nucleotide changes at positions 387, 391, 392 and 756 were in linkage in another variant haplotype. The allele frequency of UGT1A7*3 was 0.018, 0.158, 0.242, 0.433, and 0.920 in subjects carrying wild, $A(TA)_6TAA/A(TA)_7TAA$, $A(TA)_7TAA/A(TA)_7TAA$, 211G/211A, and 211A/211A variants of UGT1A1 gene, respectively. By using natural or mutagenesis primers, we successfully detected the variations at nucleotides -57, 33, 387, and 622 with the restriction enzymes *Hpy*CH4 IV, *Taq* I, *Afl* II, and *Rsa* I, respectively.

CONCLUSION: The results indicate that the allele frequencies of UGT1A7 gene in Taiwan Chinese are different from those in Caucasians and Japanese. Carriage of the nucleotide 211- variant UGT1A gene is highly associated with UGT1A7*3. The restriction-enzyme-digestion method for the determination of nucleotides -57 (or 33, or 622) and 387 can rapidly identify genotypes of UGT1A7 in an individual.

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Key words: UGT1A7 gene; Single nucleotide polymorphisms; Genotype; Taiwan Chinese

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INTRODUCTION

Polymorphisms in genes encoding drug metabolism enzymes are known to play an important role in clinical response to drug therapy and disease susceptibility[1,2]. UDP-glucuronosyltransferase enzymes (UGTs) catalyze the reaction of glucuronidation, which is one of the most important conjugative pathways for the detoxification and elimination of endogenous and exogenous compounds[2]. Polymorphisms may decrease UGT activities and cause illness in affected individuals. For instance, variant UGT1A1 genes may result in serious and benign inheritable unconjugated hyperbilirubinemia, known as Crigler-Najjar syndrome and Gilbert's syndrome, respectively[2]. Two UGT gene subfamilies, UGT1 and UGT2, have been identified in humans up to now, based on evolutional divergence[3]. Unlike the UGT2B family, which is encoded by several genes on chromosome 4q13- 21, the 13 members of UGT1 family are all derived from a single gene on chromosome 2q37 and generated by alternatively splicing of exon 1 to the four common exons (exons 2-5)[4]. The genes are designated UGT1A1 through UGT1A13 with nine functional proteins (UGT1A1, UGT1A3- UGT1A10) and four pseudogenes (UGT1A2, UGT1A11- UGT1A13), which have either nucleotide deletions or flawed TATA boxes[4].

Genetic polymorphisms of UGT1 have been described to date for only four enzymes in humans: UGT1A1[2], 1A6[5], 1A7[6], and 1A8[7].

The results of our previous study showed that the allele frequency of A $(TA)_7$TAA in the UGT1A1 gene in Taiwan Chinese was 0.143[8], comparable with that in Singaporean Chinese (0.162)[9], Malaysians (0.188)[9], and Japanese (0.1-0.168)[10-12], but lower than that in Caucasians (0.357-0.415)[13-16] and Indians (0.351)[9]. In contrast, variation rate within the coding region of UGT1A1 gene was much higher in Taiwan Chinese than that in Caucasians (0.293[8] *vs* 0.001[13]). Moreover, the key UGT1A1-gene defect for the development of neonatal hyperbilirubinemia in Japanese and Taiwan Chinese is homozygous variation at nucleotide 211[11,17,18], opposed to the homozygous variation in the promoter area, which has been reported in Caucasians[19,20]. Recently, we found a novel compound heterozygous variation of the UGT1A1 gene that caused Crigler-Najjar syndrome type 2 in a Taiwan Chinese[21]. A previous report indicated that there was a large difference in the number of UGT1A6 polymorphisms between Asians and Caucasians[5]. Those results reveal that the ethnic differences of UGT1 genes commonly occur and are worth studying.

Five and six single nucleotide polymorphisms (SNPs) have been discovered in the first exon of UGT1A7 gene in Caucasians and Japanese, respectively[6,22]. We hypothesized that the variations of UGT1A7 gene in Taiwan Chinese might be different from those in other ethnics and performed this research.

MATERIALS AND METHODS

Study subjects

Blood samples were collected from 112 healthy adult Taiwan Chinese and 505 subjects carrying different genotypes of UGT1A1 who gave their written consent to participate in this study. Among the 505 subjects, the number of different UGT1A1-genotypes carriage was 246 for wild type, 38 for A$(TA)_6$TAA/A $(TA)_7$TAA, 31 for A $(TA)_7$TAA/A $(TA)_7$TAA, 90 for 211G/211A, and 100 for 211G/211A.

Determination of SNPs

Total genomic DNA was isolated from the blood cells using the blood DNA isolation kit (Maxim Biotech Inc., San Francisco, USA). The promoter area (beginning at -114 nucleotide in the upstream) and the entire sequence of UGT1A7 exon 1 were analyzed by polymerase chain reaction (PCR). The primers used for PCR are shown in Table 1. For sequencing promoter and second part of exon 1, the forward primers were used, while for the first part of exon 1 the reverse primer was utilized. The amplification reaction mixture (100 μL) contained 1 μg of DNA in 10 mmol/L Tris-HCl (pH 8.8), 1.5 mmol/L $MgCl_2$, 50 mmol/L KCl, 0.1% Triton X-100, 200 μmol/L of each dNTP, 100 ng of each primer, and 2 U of Dynazyme DNA polymerase (Finnzymes OY, Espoo, Finland). The reaction was performed with a DNA thermal cycler (Perkin-Elmer Cetus, Norwalk, CT) as follows: three cycles of denaturation at 94 ℃ for 80 s, annealing at 55 ℃ for 60 s, and primer extension at 72 ℃ for 110 s; seven cycles of denaturation at 94 ℃ for 60 s, annealing at 55 ℃ for 60 s, and extension at 72 ℃ for 110 s; 30 cycles of denaturation at 94 ℃ for 50 s, annealing at 55 ℃ for 50 s, and extension at 72 ℃ for 90 s; and a final extension step at 72 ℃ for 10 min. The PCR products were sequenced with an automated fluorescence sequencer (ABI Prism377, PE Applied Biosystems, Foster City, CA) according to the manufacturer's instructions.

Restriction-enzyme-digestion method

We designed the natural or mutagenesis primers to detect the variant UGT1A7 genotypes found in the study subjects. PCR amplification was performed in a thermal cycler for 35 cycles of denaturation for 60 s at 94 ℃, annealing for 60 s at 55 ℃, primer extension for 60 s at 72 ℃, and a final extension for 10 min at 72 ℃. The PCR products were digested with appropriate restriction enzymes, and analyzed on 3% agarose gel (NuSieve 3: 1, FMC Bioproduct, Rockland, ME, USA) containing ethidium bromide.

Statistical analysis

The allele frequencies of UGT1A7 genotypes in our study subjects were compared with those found in Caucasians[6] and Japanese[22] by χ^2 test. For the analysis of association between UGT1A1 and UGT1A7 genes, the relative risk and its 95% confidence interval for carriage of UGT1A7*3 in the subjects bearing variant UGT1A1 gene were calculated by comparing the allele frequency of UGT1A7*3 with the subjects carrying wild UGT1A1-gene. A *P* value <0.05 was defined as statistically significant.

Table 1 Primers used for PCR and sequencing of UGT1A7 gene

Region		Primer		Target size (bp)
		Name	Sequence	
Promoter	PCR:	U7F1	5'TGAATGAATAAGTACACGCC3'	439
		U7R1	5'ATAGAGAAAATGCACTTCGC3'	
	Sequencing:	U7F1	5'TGAATGAATAAGTACACGCC3'	
Exon 1	PCR:	U7F1	5'TGAATGAATAAGTACACGCC3'	779
		U7R2	5'TAGGGGCAAAATAAATGTTC3'	
	Sequencing:	U7R2	5'TAGGGGCAAAATAAATGTTC3'	
	PCR:	U7F2	5'ATACACTCTGGAGGATCAGG3'	774
		U7R3	5'GCTACCCAACAATTAAGTGA3'	
	Sequencing:	U7F3	5'TGTCCCCAGACTTCTCTTAG3'	

bp: base pair.

RESULTS

Six SNPs at nucleotides 33 (C to A), 387 (T to G), 391 (C to A), 392 (G to A), 622 (T to C), and 756 (G to A) within the coding region of UGT1A7 exon 1 were found in the study subjects. Among them, the variations at nucleotides 33 and 756 were wobbles. The functional polymorphisms at codons 129 (nucleotide 387), 131 (nucleotide 391 or 392) and 208 (nucleotide 622) are shown in Figure 1. Incidences of UGT1A7*1/*1 (N129R131W208/N129R131W208), *1/*2 (N129R131W208/K129K131W208), *1/*3 (N129R131W208/K129K131R208), *2/*2 (K129K131W208/K129K131W208), *2/*3 (K129K131W208/K129K131R208) and *3/*3 (K129K131 R208/K129K131R208) are presented in Table 2. The incidence of UGT1A7 *1/*2 was predominant (35.7%), while that of UGT1A7 *3/*3 was the least (2.7%). As shown in Table 3, the allele frequency of UGT1A7*1 (wild type) in Taiwan Chinese was higher and that of UGT1A7*3 was lower when compared to that found in Caucasians. As compared with Japanese, the allele frequency of UGT1A7*2 was higher and that of UGT1A7*3 was lower in Taiwan Chinese.

Table 2 Frequencies of UGT1A7 genotypes in 112 Taiwan Chinese

UGTIA7	Number (%)
*1/*1	36 (32.1)
*1/*2	40 (35.7)
*1/*3	17 (15.2)
*2/*2	5 (4.5)
*2/*3	11 (9.8)
*3/*3	3 (2.7)

In addition to the six SNPs, a heterozygous or homozygous T to G conversion at nucleotide -57 in the upstream (Figure 1) was observed, which was associated with SNPs at nucleotides 33, 387, 391, 392, and 622 in one of the variant haplotypes. The nucleotide changes at positions 387, 391, 392 and 756 were in linkage in another variant haplotype. The functional variations in the 28 subjects with heterozygous T to G conversion at nucleotide -57 were UGT1A7*1/*3 in 17 and UGT1A7 *2/*3 in 11 subjects, respectively, while that in the three subjects with homozygous T to G conversion was UGT1A7*3/*3.

The distribution of the six UGT1A7 genotypes (*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3) and the UGT1A7*3 allele frequency in the subjects bearing the wild, A $(TA)_6$ TAA/A $(TA)_7$TAA, A $(TA)_7$TAA/A $(TA)_7$TAA, 211G/211A, and 211A/211A variants of UGT1A1 gene are presented in Table 4. All the subjects carrying the wild UGT1A1 gene did not bear UGT1A7*2/*3 or UGT1A7*3/*3. All the individuals bearing the variant UGT1A1 gene were at a relative higher risk for carriage of UGT1A7*3 in comparison with those with the wild type. The UGT1A7*3 allele frequency in the subjects with A$(TA)_7$AA/A $(TA)_7$TAA was not significantly different from that in analogs with A $(TA)_6$ TAA/A $(TA)_7$TAA. By contrast, the UGT1A7*3 allele frequency in the 211A/211A subjects was approximately two-fold as many as the 211G/211A analogs. Of the individuals carrying 211A/211A in UGT1A1 gene, 84% had UGT1A7*3/*3 and 16% UGT1A7*1/*3 genes, respectively.

As shown in Table 5, by using the natural or mutagenesis primers, we successfully detected the variations at nucleotides

Table 3 Allele frequencies of UGT1A7 gene among different ethnic groups

UGT1A7 alleles	Taiwan Chinese (224 chromosomes)	Caucasians (288 chromosomes)	Japanese (206 chromosomes)	*P* value (by χ^2test)
UGT1A7*1	0.576	0.358	0.593	<0.001
				0.73
UGT1A7*2	0.272	0.264	0.153	0.93
				0.004
UGT1A7*3	0.152	0.361	0.255	<0.001
				0.008

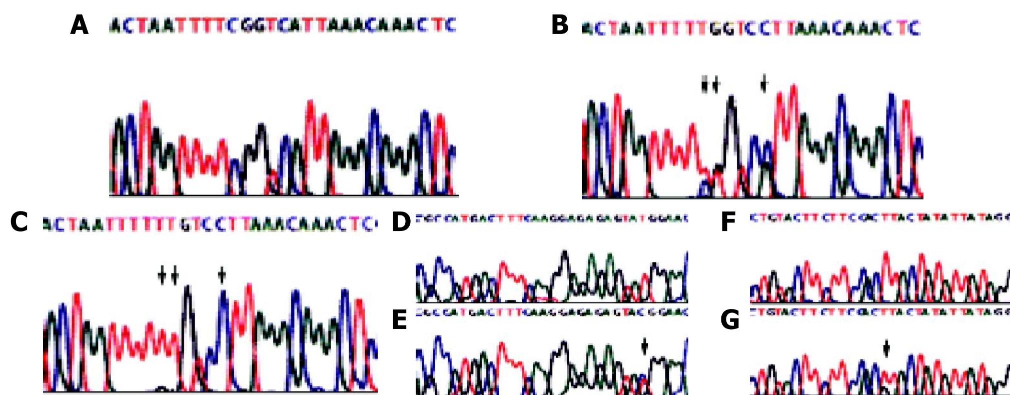

Figure 1 Representative electropherograms of (A) homozygous N^{129} R^{131} (nucleotides 387-392: TGACCG), (B) heterozygous K^{129} K^{131} (nucleotides 387-392: T/GGACC/AG/A), (C) homozygous K^{129} K^{131} (nucleotides 387- 392: GGACAA), (D) homozygous W^{208} (nucleotide 622: T), (E) heterozygous W^{208}/R^{208} (nucleotide 622: T/C), (F) - 57 T, and (G) - 57 T/G. Sequences were read reversely and nucleotides were translated into complements for (A), (B), and (C). The arrows indicate the sites of single nucleotide polymorphism.

Table 4 Allele frequency of UGT1A7*3 in subjects carrying different UGT1A1 genotypes

UGT1A1 gene	Number	UGT1A7 gene						Allele frequency of UGT1A7*3	Relative risk (95% CI)
		*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3		
Wild type	246	114	108	9	15	0	0	0.018	1.0
$A(TA)_6TAA/A(TA)_7TAA$	38	13	12	7	1	5	0	0.158	8.78^b (2.70-28.54)
$A(TA)_7TAA/A(TA)_7TAA$	31	13	5	9	1	0	3	0.242	13.44^b (4.41-40.99)
211G/211A	90	6	10	48	0	22	4	0.433	24.06^b (9.31-62.31)
211A/211A	100	0	0	16	0	0	84	0.920	51.11^b (20.24-128.80)

CI: confidence interval, ^{b}*P*<0.001 *vs* wild type.

Table 5 Natural or mutagenesis primers, restriction enzymes and the results for UGT1A7 variations

Position (cDNA)	Primers	Sequence	Restriction enzyme	Result (bp)	
-57 T→G	U7F1	5′ TGAATGAATAAGTACACGCC	HpyCH4IV	N[2]	439
	U7R1	5′ ATAGAGAAAATGCACTTCGC3′		V[3]	57+382
33 C→A	1stPCR				
	U7F1	5′ TGAATGAATAAGTACACGCC			
	U7R2	5′ TAGGGGCAAAAAATGTTC3′			
	2ndPCR				
	U7-33F1	5′ GGGTGGACTGGCCTCCT<u>G</u>3′[1]	Taq I	N	115
	U7-33R	5′ ACTGCATGGTGAACCAGTCG		V	19+96
387 T→G	1stPCR				
	U7F1	5′ TGAATGAATAAGTACACGCC			
	U7R2	5′ TAGGGGCAAAATAAATGTTC			
	2ndPCR				
	U7-387F	5′ AAATTGCAGGAGTT<u>CT</u>TA3′[1]	Afl II	N	159
	U7-387R	5′ TGGCAAAATATTCCCCGC3′		V	140+19
622 T→C	U7F3	5′ TGTCCCCAGACTTCTCTTAG	Rsa I	N	447
	U7R3	5′ GCTACCCAACAATTAAGTGA		V	54+393

bp: base pair, [1]mutagenesis site, [2]N: digestion result of wild type, [3]V: digestion result of variant.

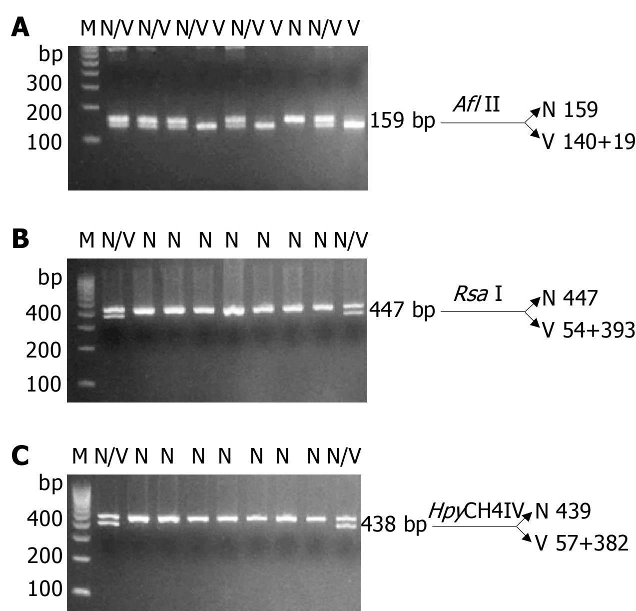

Figure 2 Results of restriction fragments at nucleotides (A) 387, (B) 622, and (C) -57, digested by *Afl* II, *Rsa* I, and *Hpy*CH4 IV, respectively. The bands of 19, 54, and 57 bp were too small to be seen (bp = base pair, M: DNA size marker, N: wild type, V: variant).

-57, 33, 387, and 622 with restriction enzymes *Hpy*CH4 IV, *Taq* I, *Afl* II, and *Rsa* I, respectively. The example products are shown in Figure 2.

DISCUSSION

In the studies of SNPs for UGT1 in general populations, most data were focused on UGT1A1 gene. Four common allelic variations in the TATA box of UGT1A1 promoter have been observed[13-16]. In addition, within the coding region of UGT1A1 gene, the variations at nucleotides 211, 686, 1 091, 1 099, and 1 456 have been found in Asians[8,10-12,17,18,23,24]. The other SNPs in UGT1 ever described are limited to UGT1A6, UGT1A7, and UGT1A8. For UGT1A6 gene, two close missense variations have been reported[5]. For UGT1A8 gene, four genotypes have been observed[7]. Recently, six SNPs in UGT1A7 have been identified[6,22]. There were missense variations in codons 129, 131, and 208, characterized by the substitution of N for K, R for K, and W for R, respectively. The allele containing all three missense variations, UGT1A7*3, was found exhibiting a 5.8 fold lower relative activity compared to the wild type[6].

UGT1A7 is a typical isoenzyme of the extrahepatic

UGT, with undetectable expression transcript in human liver[25], while it is differentially expressed in human lung[6], esophagus[26], and stomach[27]. The main substrates conjugated by UGT1A7 are some phenolic compounds, carcinogens, and drugs[28,29]. In the studies of disease susceptibility for Caucasians, UGT1A7*3 was found to be a risk gene for the development of orolaryngeal cancer[30], hepatocellular carcinoma[31], and colorectal cancer[27]. UGT1A7 might characterize a "trans-acting modifier gene" of cancer at the liver as well as at other sites of the body[27,31]. However, population study is the first step to set up the basic data for every ethnic. That is why we performed this research.

All the five and six SNPs of UGT1A7 observed in Caucasians and Japanese[6,22] were found in Taiwan Chinese. However, the allele frequencies of UGT1A7 were different among Taiwan Chinese, Caucasians, and Japanese. The low activity of UGT1A7*3/*3, which exists in a considerable proportion of population (15.3%) in Caucasians[6], was identified only in 2.7% in our study subjects. The clinical significance of this difference warrants further investigation since hepatocellular carcinoma, one of UGT1A7*3-related sicknesses, is still a life-threatening disease in Taiwan[32]. The UGT1A7*4 allele (N129R131R208), with 0.017 in frequency in Caucasians[6], was not found in our study subjects. The variation at nucleotide -57 in the upstream of UGT1A7 gene is a novel finding. The association between this variation and SNPs at nucleotides 33, 387, 391, 392, and 622, as well as the association of nucleotides 387, 391, 392, and 756 in another haplotype, might be a founder effect. Our results also indicate that the UGT1A1 gene variant at nucleotide 211 was highly associated with carriage of UGT1A7*3. However, it remains possible that this phenomenon may be a founder effect. The results of our previous studies revealed that homozygous variation at nucleotide 211 of UGT1A1 gene was a risk factor for developing hyperbilirubinemia[17,18]. If UGT1A7*3 is a risk SNP for the development of certain cancers, the interaction between UGT1A1 211A/211A and UGT1A7*3, serum bilirubin level, and its effect on disease severity in patients are worthy of investigation. Interestingly, the 211 G to A variation has been found in Japanese, Koreans, Chinese[11], and Taiwan Chinese[8,17,18], but not in Caucasians[13]. This suggests that the clinical significance of the association between UGT1A1 211A/211A and UGT1A7*3 is more important for the Orientals.

The rapid restriction-enzyme-digestion method for the detection of nucleotide -57 (or 33, or 622) can identify the genotypes of UGT1A7*3/*3 in an individual. The genotype is UGT1A7*3/*3 if the result is homozygous G at nucleotide -57 (or homozygous A at nucleotide 33, or homozygous C at nucleotide 622). The Afl II-digestion-method for nucleotide 387, following the detection of nucleotide -57 (or 33, or 622), can identify the genotypes in subjects carrying genes other than UGT1A7*3/*3. In the situation of wild type at nucleotide -57 (or 33, or 622), the genotypes are UGT1A7 *1/*1, *1/*2, and *2/*2 when the results of nucleotide 387 are wild, heterozygous variation, and homozygous variation, respectively. In the situation of heterozygous variation at nucleotide -57 (or 33, or 622), the genotypes are UGT1A7 *1/*3 and *2/*3 when the results of nucleotide 387 are heterozygous and homozygous variations, respectively. Therefore, the restriction-enzyme-digestion method for the determination of nucleotides -57 (or 33, or 622) and 387 can rapidly identify the genotypes of UGT1A7 in an individual.

In conclusion, the features of UGT1A7 gene are found in Taiwan Chinese and a simple and rapid method to determine genotypes of UGT1A7 is established. The clinical studies for this important gene are on-going.

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