Linkage disequilibrium of *UGT1A1*6* and *UGT1A1*28* in relation to *UGT1A6* and *UGT1A7* polymorphisms

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Abstract. UDP-glucuronosyltransferase (UGT) enzymes are responsible for the glucuronidation and detoxification of many endogenous or exogenous xenobiotics. Gilbert's syndrome (GS) and Crigler Najjar syndrome type 2 (CNS-II) are characterized by unconjugated hyperbilirubinemia due to reduced enzymatic activity of *UGT1A1*. Recent studies have demonstrated the frequent co-existence of *UGT1A1*28* (-53 $[TA]_{6>7}$) with other polymorphisms of *UGT1A6* and *UGT1A7*. This finding suggests the occurrence of linkage disequilibrium (LD) among *UGT1A1*, *UGT1A6* and *UGT1A7* polymorphisms. *UGT1A1*6* (211G>A, G71R) and *UGT1A1*28* are common in Asian populations. In the present study, we investigated the LD of *UGT1A1*6* and *UGT1A1*28* in relation to *UGT1A6* and *UGT1A7* polymorphisms. Exon 1 of *UGT1A1*, *UGT1A6* and *UGT1A7* was sequenced using genomic DNA isolated from peripheral leukocytes of 390 Japanese subjects. LD and haplotypes were analyzed using SNPAlyze ver. 5.0 software. *UGT1A1*6* had a strong LD in relation to *UGT1A6* variants including 541A>G and 552A>C (D'=0.846-0.848, r^2=0.413-0.438) and *UGT1A7* variants including 387T>G, 391C>A, 392G>A and 622T>C (D'=0.667-0.858, r^2=0.207-0.413). *UGT1A1*28* had a lower degree of LD than *UGT1A1*6* in relation to these variants (D'=0.245-0.401, r^2=0.025-0.063). All the haplotypes with G71R lacked -53$[TA]_{6>7}$. The present study showed for the first time that the LD of *UGT1A1*6* in relation to *UGT1A6* and *1A7* polymorphisms is far stronger than *UGT1A1*28*. The *UGT1A1*6* allele appears to be independent of the *UGT1A1*28* allele. Although patients with GS and CNS-II are believed to have good prognosis, a subgroup of GS or CNS-II patients with the *UGT1A1*6* polymorphism might be at risk of abnormal drug metabolism and of developing malignant disease.

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Abbreviations: CNS-II, Crigler-Najjar syndrome type II; GS, Gilbert's syndrome; LD, linkage disequilibrium; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-f]pyridine; RT-PCR, reverse transcription-polymerase chain reaction; STB, serum total bilirubin; UGT, UDP-glucuronosyltransferase

Key words: Gilbert's syndrome, Crigler Najjar syndrome, haplotype, carcinogenesis, drug metabolism

Introduction

UDP-glucuronosyltransferase (UGT) enzymes are responsible for the glucuronidation and detoxification of many xenobiotics including a large variety of carcinogens and endogenous compounds (1). UGTs (UGT1 and UGT2) have been categorized into two families according to their sequence homology and substrate specificity. The *UGT1* gene is located on chromosome 2q37, and it encodes nine functional proteins (*UGT1A1*, *UGT1A3-1A10*); the chromosomal locus also contains four pseudogenes (*UGT1A2p*, *UGT1A11p-13p*) (2) (Fig. 1).

UGT1A1 plays a critical role in the detoxification of neurotoxic bilirubin. Reduced *UGT1A1* activity causes unconjugated hyperbilirubinemia and this condition has been categorized in several clinical syndromes including Crigler-Najjar syndrome (CNS) and Gilbert's syndrome (GS) (3,4). Serum total bilirubin (SBT) is less than 108.6 μmol/l in GS but it is higher than this level in CNS. Numerous polymorphisms of *UGT1A1* have been reported in patients with CNS and GS. Differences in *UGT1A1* allele frequencies between Caucasians and Asians are well established (5), with the *UGT1A1*28* (-53$[TA]_{6>7}$) allele being less frequent in Asians and *UGT1A1*6* (221G>A, G71R) being rare in Caucasians but common in Asians. The allelic frequency of *UGT1A1*28* in the normal Japanese population is 0.11 (6), whereas that of *UGT1A1*6* is between 0.183 and 0.23 in the Asian population (5-8). The enzymatic activity of *UGT1A1*6* protein is reduced to 40% of the wild-type *UGT1A1* (9). A significant decrease in the *UGT1A1* protein level and bilirubin conjugation activity was reported in subjects with homozygous *UGT1A1*28* compared with subjects with homozygous *UGT1A1*1* (10).

UGT1A6 is an important UGT isozyme that catalyzes the glucuronidation of small phenolic drugs such as aceta-

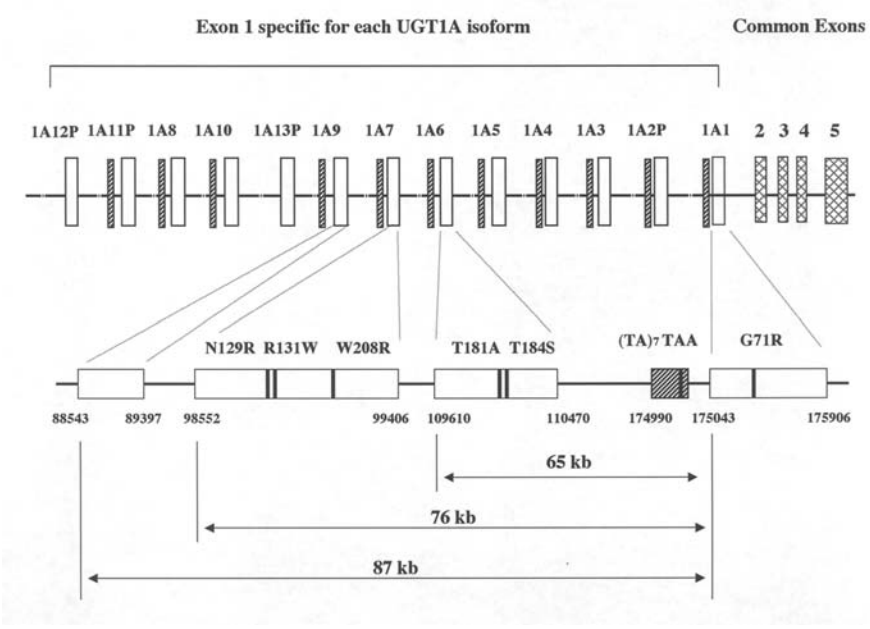

Figure 1. *UGT1A7*, *UGT1A6* and *UGT1A1* variants in the present study population. Nucleotide numbers are in accord with the number of *Homo Sapiens UGT1A* gene locus (GenBank accession no. AF297093). The TATA box is shaded.

minophen. Several *UGT1A6* polymorphisms, from *UGT1A6*1* to *1A6*4*, have been identified (11). A missense mutation of *UGT1A6* was associated with less protective action of aspirin against colon adenoma (12).

UGT1A7 is responsible for glucuronidating benzo(alpha)-pyrene metabolites, heterocyclic amines and therapeutic drugs including camptothecin metabolites (13). A reduction of this function in the genetic variant *UGT1A7*3* (387T>G/391C>A/392G>A/622T>C, N129K/R131K/W208R) has been linked with a risk for developing cancer of the orolaryngeal tract (14), the lung (15), colon (16), liver (17,18) and pancreas (19). In all of these cases, cancer is related to the exposure to mutagens. The enzymatic activity of *UGT1A7*3* toward benzo(alpha)pyrene metabolites is reduced to 17% in comparison with the wild-type *UGT1A7*1* (100%) (20).

Recent studies have shown that *UGT1A1*28*, *UGT1A6*2* and *UGT1A7*3* polymorphisms frequently coexist, suggesting a linkage disequilibrium (LD) of *UGT1A1*28* in relation to *UGT1A6* and *UGT1A7* variants (21). However, the LD of *UGT1A1* polymorphisms including *UGT1A1*6* in relation to *1A6* and *1A7* is not completely clear. To clarify this point, we investigated the LD among the *UGT1A1*, *UGT1A6* and *UGT1A7* variants.

Materials and methods

Study population and isolation of genomic DNA. Three hundred and ninety Japanese individuals (235 males and 155 females, mean age 44.5 years) were enrolled in this study. There were 81 (44 males and 37 females, mean age 22.3 years) subjects with GS or CNS type 2 (CNS-II). The mean STB level was 38.7 and 139.4 μmol/l in GS and CNS-II groups, respectively. Among the remaining 309 subjects, there were 113 patients with lung cancer (78 males and 35 females, mean age 57.9 years) and 196 healthy individuals (113 males and 83 females, mean age 34.2 years). A frequent occurrence of *UGT1A7*3* in lung cancer has been reported in the Japanese population (14). The presence of *UGT1A1* polymorphism had not been previously evaluated in our 309 subjects. Informed consent was obtained from all subjects. The study was approved by the Ethics Committee of Mie University Graduate School of Medicine.

Extraction of genomic DNA and amplification of UGT1A7. Genomic DNA was isolated from peripheral leukocytes using DNAQuick (Dai-Nippon Phram. Co. Ltd., Osaka, Japan) according to the manufacturer's instructions. TATA box of *UGT1A1* and exon 1 of *UGT1A1*, *UGT1A6* and of *UGT1A7* were amplified by polymerase chain reaction (PCR). The primers used for specific amplification are listed in Table I. CR mixtures were incubated at 94˚C for 2 min, and then PCR was performed at 94 ˚C for 1 min, 58 ˚C for 1 min, and 72 ˚C for 2 min, during 30 cycles. A final extension at 72˚C for 8 min was performed to ensure complete extension of the PCR products.

Sequence of the PCR product. The PCR products were directly sequenced by a dye terminating method using the ABI PRISM genetic analyzer (PE Applied Biosystems, Foster city, CA, USA). The sequences of the primers used are listed in Table I.

Statistical analysis. Comparison of the allelic frequencies was performed using the Chi-square test. P-values <0.05 were considered as statistically significant. Hardy-Weinberg equilibrium, pairwise D' and r^2 values in LD and the haplotype block among *UGT1A1*, *UGT1A6* and *UGT1A7* variants were analyzed using SNPAlyze software ver. 5.0 (Dynacom, Chiba, Japan). P-values ≥0.05 were considered as significantly deviated from the Hardy-Weinberg equilibrium.

Table I. PCR primers.

Primers	Sequence (5'-3')	GenBank accession no./ mapping position
UGT1A1		AF297093
forward	ACACTTGTTGGTCTGTG	174734-174756
reverse	GCTTGCTCAGCATATATCTGGG	175999-175978
sequence 1	ACGATGGGGCTGCAA	175521-175507
sequence 2	GTAGGAGAGGGCGAACC	175005-175021
UGT1A6		AF297093
forward	TGACCAAGAAGAGCTGAAGAAC	109833-109855
reverse	GTAGCACCTGGGAATGTAGGAC	110197-110176
sequence 1	TGACCAAGAAGAGCTGAAGAAC	109855-109876
UGT1A7		AF297093
forward	CGTCAAGGCCAAAAGCAT	98246-98263
reverse	AAGAGCTGCTTTATACAATTTGCAA	99561-99585
sequence 1	CAGCACAGGGCATGATCT	98296-98313
sequence 2	AGTTCATGGTTTTTGCCGAT	98817-98836

Table II. Frequency of *UGT1A1*, *UGT1A6* and *UGT1A7* alleles.

	UGT1A1		*UGT1A6*		*UGT1A7*		
	-53[TA]$_{6>7}$	211G>A	541A>G	552A<C	387t>G	391C>A/ 392G>A	622T<C
Frequency	0.167	0.223	0.319	0.339	0.382	0.382	0.304
No. of allele (2n=780)	130	174	249	264	298	298	237
P-value	<0.001	0.54	0.60	0.96	0.04	0.04	0.55

P-values <0.05 were considered in the Hardy-Weinberg equilibrium.

Results

Allelic frequency of UGT1A1, UGT1A6 and UGT1A7 polymorphisms. Allelic frequency of *UGT1A1*, *1A6* and *1A7* polymorphisms are described in Table II. In the present study, 137 (0.17) and 174 (0.22) out of 760 alleles had -53 [TA]$_{6>7}$ and 211G>A in *UGT1A1*, respectively. The allelic frequency of -53[TA]$_{6>7}$ observed in the present study was significantly higher than the data previously reported in normal Japanese population (0.11) (P<0.01) (8). The variants of -53[TA]$_{6>7}$, 387T>G and 391C>A/392G>A were in the Hardy-Weinberg equilibrium (P<0.05).The remaining variants were out of the Hardy-Weinberg equilibrium (P-value of 0.54-0.96) (Table II).

Linkage disequilibrium of UGT1A1 in relation toUGT1A6 and UGT1A7. The 221G>A had a strong LD with the *UGT1A6* polymorphism (D' values from 0.846-0.858, r^2 values from 0.413-0.438) (Fig. 2). Between the 221G>A and the *UGT1A7* polymorphism, the highest D' value was observed between the 221G>A variant and 552A>C (D' value of 0.858), whereas the highest r^2 value was observed between the 221G>A variant and 541A>G (r^2 value of 0.438). The 221G>A also had a strong LD with *UGT1A7* (D' values from 0.667-0.766, r^2 values from 0.207-0.386). The 221G>A was more strongly associated with the *UGT1A6* polymorphisms than with the *UGT1A7* polymorphisms.

In contrast, the -53[TA]$_{6>7}$ variant had a lower degree of LD in relation to *UGT1A6* (D' values from 0.289-0.401, r^2 values from 0.036-0.062) and *UGT1A7* (D' values from 0.245-0.276, r^2 values from 0.025-0.028). Interestingly, there was no LD between the 221G>A and -53[TA]$_{6>7}$ (D' value of -1) (Fig. 2).

Linkage disequilibrium between UGT1A6 and UGT1A7. Among the *UGT1A6* variants, strong LD was observed

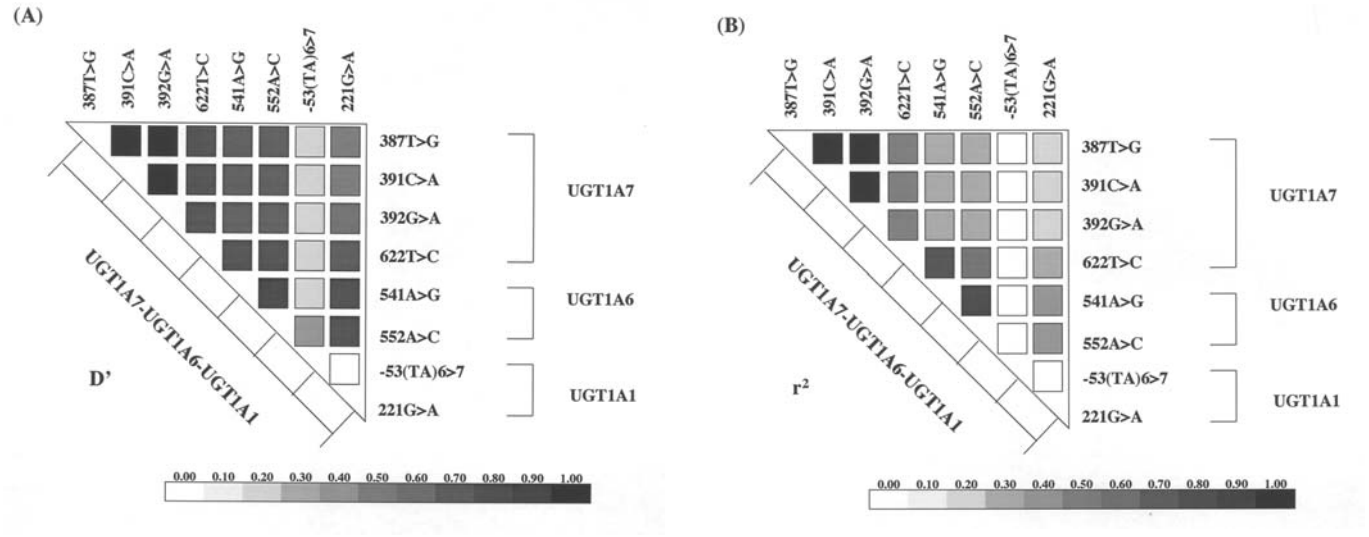

Figure 2. Linkage disequilibrium among *UGT1A7*, *UGT1A6* and *UGT1A1* variants. The D' values (A) and the r^2 values (B) were analyzed using SNPAlyze software ver. 5.0 (Dynacom).

Table III. Main haplotype frequencies.

Haplotype number	Haplotype							Frequency (2n=780)
	UGT1A1		*UGT1A6*		*UGT1A7*			
	-53	211	541	552	387	391/392	622	
1	TA_6	G	A	A	T	C/G	T	48.49
2	TA_6	A	G	C	G	A/A	T	16.71
3	TA_6	G	A	A	G	A/A	T	7.07
4	TA_7	G	G	C	G	A/A	C	6.68
5	TA_7	G	A	A	T	C/G	T	6.57
6	TA_6	G	G	C	G	A/A	C	2.59
7	TA_6	A	G	C	T	C/G	C	1.52
8	TA_6	A	A	A	T	C/G	T	1.42
9	TA_6	G	A	A	G	A/A	C	1.27
10	TA_6	A	G	C	T	C/G	T	1.18
11	TA_7	G	G	C	T	C/G	T	1.13
12	TA_7	G	A	C	G	A/A	T	1.03

between 541A>G and 552A>C (D' value of 1, r^2 value of 0.917) (Fig. 2). Among the *UGT1A7* variants, 387T>G, 391C<A and 392G>A were constantly associated (D' value of 1, r^2 value of 1). The 622T>C variant had a strong LD with 387T>G, 391C<A and 392G>A (D' value of 0.895, r^2 value of 0.566). A high degree of LD was observed between the *UGT1A6* and *UGT1A7* polymorphisms (D' values from 0.753-0.884, r^2 values from 0.430-0.727) (Fig. 2).

Haplotype analysis. Twenty-six haplotypes were found in the present study (data not shown), 12 of which had a frequency of more than 1% (Table III). The most frequent haplotype in the G71R (*UGT1A1*6*) variants was haplotype 2 (*UGT1A1*6/UGT1A6*2/UGT1A7*3*, frequency of 16.71%). Haplotypes 7 (*UGT1A1*6/UGT1A6*2/UGT1A7*4*), 8 (*UGT1A1*6/UGT1A6*1/UGT1A7*1*) and 10 (*UGT1A1*6/UGT1A6*2/UGT1A7*1*) had frequencies of more than 1% (1.18%-1.52%). All the haplotypes with 211G>A (8 haplotypes) lacked -53 $[TA]_{6>7}$.

Discussion

The present study investigated the occurrence of LD among *UGT1A1*, *UGT1A6* and *UGT1A7* polymorphisms in the Japanese population and we found that *UGT1A1*6* had a strong LD in relation to *UGT1A6* and *1A7* polymorphisms.

As *UGT1A1*6* is common in Asians, such an interesting LD was elucidated in Japanese subjects. It is worth noting that the subjects enrolled in our present investigation are considerably different from the normal Japanese population; we collected DNA samples from 81 GS or CNS-II patients, 113 lung cancer patients and 196 unscreened healthy individuals. GS or CNS-II patients frequently have *UGT1A1* polymorphisms, whereas those with lung cancer frequently have *UGT1A7* polymorphisms. Our present study population is significantly deviated from the Hardy-Weinberg equilibrium and has an increased frequency of the *UGT1A1*28* allele as compared to data previously reported in a normal Japanese population. We expect an increased frequency of variations in patients with diseases resulting in a departure from the Hardy-Weinberg equilibrium.

Both *UGT1A1*28* and *UGT1A1*6* are relatively frequent alleles in the Asian populations; however, no subject with both haplotypes was found in the present study. This finding suggests that the *UGT1A1*28* allele is different from the *UGT1A1*6*.

The present study showed that haplotypes with *UGT1A1*28/UGT1A6*2/UGT1A7*3* (haplotype no. 4 in Table III) have a frequency of 6.68%. This result is consistent with previously reported data showing frequent co-existence of *UGT1A1*28*, *UGT1A6*2* and *UGT1A7*3* polymorphisms (21). In the present study, the frequency of the combination of -53$[TA]_{6>7}$ with the wild-types of *UGT1A6* and *UGT1A7* (haplotype no. 5, *UGT1A1*28/UGT1A6*1/UGT1A7*1*) was found to be similar to that of haplotype no. 4. In contrast, the frequency of haplotype no. 2 (*UGT1A1*6/UGT1A6*2/UGT1A7*3*) was 74.6% in all haplotypes with 211G>A variants. This may result in a higher LD of *UGT1A1*6* in relation to *UGT1A6* and *UGT1A7* variants than between *UGT1A1*28* and *UGT1A6* or *UGT1A7* variants.

Strong LD was observed within the *UGT1A6* and *UGT1A7* polymorphisms. These loci are approximately 11-kb distant. However, there was a strong LD between *UGT1A1* and *UGT1A6/UGT1A7* despite their far distant loci; exon 1 of *UGT1A6* and *UGT1A7* is approximately 65-kb and 76-kb distant from that of *UGT1A1*, respectively (Fig. 1). Innocenti *et al* recently reported the LD between *UGT1A1* and *UGT1A9* in Caucasians and Asians (22). They found D' values of 0.39-0.93 and r^2 values of 0.01-0.15 with regard to the LD between the -118 *UGT1A9* and *UGT1A1* variants in Asians. Although the exact haplotype structure and LD pattern across the entire *UGT1A* locus has not yet been established, these findings suggest that the LD among the common variants extends from *UGT1A1* through *UGT1A9* (Fig. 1) with a distance of 87 kb. It is interesting that the r^2 value between *UGT1A1* and *UGT1A9* is relatively lower compared with that between *UGT1A1* and *UGT1A6* or *UGT1A7*. These observations suggest that the degree of LD might be associated with the distance between the loci.

It is generally believed that GS or CNS-II patients have good prognosis. However, Girad *et al* recently reported that *UGT1A1* polymorphisms are an important determinant of the degree of dietary carcinogen detoxification (23). They assessed only the *UGT1A*28* and they did not evaluate the *UGT1A1*6*. However, the LD across the *UGT1* locus observed in our present study suggests that GS or CNS-II patients with *UGT1A1*6* might have an abnormal metabolism of cytotoxic drugs such as irinotecan and thus may be at risk of developing malignant disease.

In summary, the present study showed for the first time that the LD of *UGT1A1*6* in relation to the *UGT1A6* and *1A7* polymorphisms is far stronger than *UGT1A1*28*. Although patients with GS and CNS-II are believed to have good prognosis, the strong LD among *UGT1A1*, *1A6* and *1A7* polymorphisms suggests that a subgroup of GS or CNS-II patients with the *UGT1A1*6* polymorphism might be at risk of abnormal drug metabolism and developing malignant disease.

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