PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

ELSEVIER

World J Gastroenterol 2005;11(21):3250-3254
World Journal of Gastroenterology ISSN 1007-9327

• *COLORECTAL CANCER* •

Link between colorectal cancer and polymorphisms in the uridine-diphosphoglucuronosyltransferase *1A7* and *1A1* genes

Kung-Sheng Tang, Hui-Fen Chiu, Hong-Hwa Chen, Hock-Liew Eng, Chia-Jung Tsai, Hsiu-Chen Teng, Ching-Shan Huang

Kung-Sheng Tang, Department of Medical Technology, Fooyin University, Kaohsiung, Taiwan; Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, China
Hui-Fen Chiu, Graduate Institute of Medicine and Department of Pharmacology, Kaohsiung Medical University, Kaohsiung, Taiwan, China
Hong-Hwa Chen, Department of Colorectal Surgery, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, China
Hock-Liew Eng, Chia-Jung Tsai, Department of Pathology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan, China
Hsiu-Chen Teng, Department of Medical Management, Fooyin University, Kaohsiung, Taiwan, China
Ching-Shan Huang, Department of Medical Technology, Fooyin University, Kaohsiung, Taiwan; Department of Laboratory Medicine, Cathay General Hospital, Taipei, Taiwan, China
Supported by a Grant From the National Science Council (NSC 93-3112-B-242-001), Taipei, Taiwan, China
Correspondence to: Professor Ching-Shan Huang, Department of Medical Technology, Fooyin University, 151 Chin-Hsueh Road, Ta-Liao Hsiang, Kaohsiung Hsien 831, Taiwan; Department of Laboratory Medicine, Cathay General Hospital, 280, Jen Ai-Road, Section 4, Taipei 106, Taiwan, China. chsh.huang@msa.hinet.net
Telephone: +886-22-6360450 Fax: +886-28-7725983
Received: 2004-10-29 Accepted: 2004-12-01

Abstract

AIM: To investigate the relationship between single nucleotide polymorphisms in the uridine-diphosphoglucuronosyltransferase (UGT) *UGT1A7* and *UGT1A1* genes and patients suffering from colorectal cancer (CRC).

METHODS: A case-control study was designed in order to investigate the genotypes of the *UGT1A7* and *UGT1A1* genes, which were identified by the polymerase chain reaction-restriction fragment length polymorphism (RFLP) method, for 268 CRC patients and 441 healthy controls.

RESULTS: The results of simple logistical regressions revealed odds ratios (ORs) of 1.97 ($P<0.001$), 1.91 ($P<0.001$), and 2.03 ($P<0.001$) for patients who carried the *UGT1A7*1/*3* genotype, *UGT1A7*3* allele, and variant-211 *UGT1A1* allele. The interaction of *UGT1A7*3* allele and variant-211 *UGT1A1* allele produced an additive effect on the risk for the development of CRC [observed OR (2.34) greater than expected OR (1.59)]. For the 268 patients, the results of simple logistical regressions indicated that the OR of developing metastases was 4.90 ($P<0.001$) and 4.89 ($P<0.001$) for the individuals possessing *UGT1A7*3* allele and variant-211 *UGT1A1* allele, respectively. The results of multivariate logistical regressions confirmed these findings (OR = 2.51, $P = 0.01$; and OR = 2.71, $P = 0.01$, respectively). The interaction of these two variants resulted in an additive effect on the risk for metastases amongst patients [observed OR (6.83) greater than expected OR (4.56)].

CONCLUSION: In conclusion, carriage of the *UGT1A7*3* allele, as well as variant-211 *UGT1A1* allele represents a risk factor for the development of, and a determinant for, metastases associated with CRC patients.

Key words: Colorectal cancer; *UGT1A7*3* allele; Variant-211 *UGT1A1* allele; Metastases

Tang KS, Chiu HF, Chen HH, Eng HL, Tsai CJ, Teng HC, Huang CS. Link between colorectal cancer and polymorphisms in the uridine-diphosphoglucuronosyltransferase *1A7* and *1A1* genes. *World J Gastroenterol* 2005; 11(21): 3250-3254
http://www.wjgnet.com/1007-9327/11/3250.asp

INTRODUCTION

The uridine-diphosphoglucuronosyltransferase (UGT) superfamily is a detoxification pathway[1]. Two subfamilies, UGT 1 and UGT 2, have been identified in human bodies[2]. The study concerns the single nucleotide polymorphisms (SNPs) in the UGT 1 subfamily. Recently, in determining the full sequence of the *UGT1A1* and *UGT1A7* genes, we have observed that the allele frequencies of both the genes for our populations differed from the corresponding figures for Caucasians[3]. We also found that carriage of the variant *UGT1A1* gene at nucleotide 211 [211 G to A (G71R)] was highly associated with the carriage of *UGT1A7*3* allele. The *UGT1A7*3* allele in Caucasian populations has been shown to be a risk factor in cancer of oral cavity[4], liver[5], colon[6] and pancreas[7], which are included as leading causes of cancer mortality in Taiwan[8]. This study is a case-controlled research of the variants for the *UGT1A7* and *UGT1A1* genes in patients from Taiwan with colorectal cancer (CRC). This is probably the first report conducted to research the relative risk for the development of CRC simultaneously for these two genes.

MATERIALS AND METHODS

Patients and controls

The study subjects consisted of 268 pathologically-identified CRC patients collected between January 2004 and July 2004

and 441 healthy controls who attended our institution for the purpose of a physical examination during the same period. All study-participating individuals provided their written consent as regards their participation. All the 268 CRC patients underwent surgery followed by subsequent pathological examination for tumor residue/presence within a period of about 2 mo subsequent to initial diagnosis at which time the suspicious symptoms were first noticed. The tumor was diagnosed by pathological observation and categorization into one of the several tumor-developmental stages A-D, according to the criteria of the modified Dukes classification scale: stage A, limited to mucosa; stage B, extension into, R/O through muscularis propria, no nodal involvement; stage C, limited or substantial extension through bowel wall, metastases in the lymph nodes; and stage D, distant metastases[9].

Determination of UGT1A7 and UGT1A1 genotypes

Total genomic DNA was isolated from peripheral blood cells (K_3EDTA as anticoagulant) using the blood DNA isolation kit (Maxim Biotech Inc., San Francisco, CA, USA). PCR amplification was performed in a thermal cycler (Perkin-Elmer Cetus, Norwalk, CT, USA) applying 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 genotypes of *UGT1A7* were identified by determining nucleotides -57 and 387 with the restriction fragment length polymorphism (RFLP) method, using enzymes HpyCH4 IV and *Afl*II as described previously. If the result is a homozygous G variation at nucleotide -57, the genotype is *UGT1A7*3/*3*. The detection of nucleotide 387, following the determination of nucleotide -57, can be used as a marker to identify the genotypes of *UGT1A7* in subjects carrying genes other than *UGT1A7*3/*3*. For the situation for the wild type of *UGT1A7* gene at nucleotide -57, the genotypes are *UGT1A7*1/*1*, **1/*2*, and **2/*2* when the results for nucleotide 387 show it to be wild, heterozygous variation, and homozygous variation. For the situation, where there exists heterozygous variation at nucleotide -57, the genotypes are, respectively, *UGT1A7*1/*3* and **2/*3* when the results for nucleotide 387 reveal heterozygous and homozygous variations. For the determination of the *UGT1A1* gene, the promoter area and nucleotides 211, 686, 1 091, and 1 456 were analyzed using the RFLP method as described previously[10]. In brief, the restriction enzymes *Ava*II, *Bsr*I, *Bcl*I, and *Ava*II were utilized in order to determine whether heterozygous and homozygous variations occur at nucleotides 211, 686, 1 091, and 1 456; while the $A(TA)_6TAA$ and $A(TA)_7TAA$ of the promoter area were differentiated directly by the size of the produced PCR fragments (77 and 79 bp, respectively) on the electrophoresed agarose gel. The DNAs of *UGT1A7*1/*1*, **1/*2*, *1/*3*, **2/*2**, **2/*3*, **3/*3*, and the five known variants (promoter area and nucleotides 211, 686, 1 091, and 1 456) in the *UGT1A1* gene (heterozygous and homozygous), which had been found and identified by the DNA sequencing method, respectively[3], were run as controls in each performance of genotyping assays by the RFLP method.

Statistical analysis

The χ^2 test and Student's *t*-test were used, as appropriate, in order to compare parameters corresponding to the case and control groups. To evaluate the contribution of each genetic allele, simple and multivariate logistical regressions, as appropriate, were used for the calculation of the relevant odds ratio (OR) and the 95%CI for CRC. The respective ORs for developing metastases (stages C and D) CRCs for the subjects carrying CRC-related *UGT1A* alleles were compared with the corresponding values for patients not bearing those alleles. Interaction effects between suspected risk factors were evaluated using the logistical regression models. The evaluation of the dimension of interaction was then performed by comparing observed with expected ORs under the assumptions derived from the application of additive models[11]. A P value <0.05 or a 95%CI for the OR above or below 1.0 was defined as constituting statistical significance. All data were analyzed using the Statistical Package for Social Sciences software (SPSS, version 10.0; SPSS Inc., Chicago, IL, USA).

RESULTS

For both the case and control groups, the male/female ratio was identical (140/128 *vs* 237/204, $P = 0.70$ by χ^2 test, data not shown in the tables), whilst the mean age was significantly different (65±11.2 years, range 31-92 years *vs* 47.0±12.3 years, range 20-79 years, $P<0.001$ by Student's *t*-test, data not shown in the tables). Six genotypes and three alleles of the *UGT1A7* gene were found in both case and control groups, as shown in Table 1. Table 1 also reveals that about half decreased and two-fold increased in the risk of individuals developing CRC existed for subjects who carried the *UGT1A7*1/*1* (wild type) and *UGT1A7*1/*3* genotypes, respectively (OR = 0.55, $P<0.001$; and OR = 1.97, $P<0.001$), whilst the ORs for those possessing genotypes *UGT1A7*1/*2*, *UGT1A7*2/*2*, *UGT1A7*2/*3*, and *UGT1A7*3/*3* did not prove to be meaningful. Table 2 shows that the frequency distribution of *UGT1A7* genotypes in our control group followed the Hardy-Weinberg equilibrium. Four of the five variant alleles determined for the *UGT1A1* gene were found in both the case and control groups, whilst the allele for the variation at nucleotide 1 456 was neither observed in the case nor in the control group, as shown in Table 3. The incidence for variant *UGT1A1* gene was not significantly different between the case and control groups ($P = 0.78$). Table 3 also shows that the frequency distribution of *UGT1A1* genotypes in our control group followed the Hardy-Weinberg equilibrium. The analysis for the genetic alleles, as listed in Tables 1 and 4, indicated that only the ORs of *UGT1A7*3* allele and variant-211 allele in the *UGT1A1* gene were statistically significant between the case and control groups (1.91, $P<0.001$; and 2.03, $P<0.001$, respectively). Since the mean age was significantly different between the case and control groups, the multivariate logistical regressions were not performed to analyze the adjusted ORs for age, gender, and the CRC-related *UGT1A* alleles. The interaction of *UGT1A7*3* allele and variant-211 *UGT1A1* allele revealed an additive effect on the risk for the development of CRC, as the observed OR (2.34) was greater than the expected OR (1.59) between the case and control groups, as shown

in Table 5. Table 6 illustrates the relationship between the stage of CRC and the presence of the CRC-related *UGT1A* alleles. The two stage-D patients possessed both *UGT1A7*3* and variant-211 *UGT1A1* alleles, whilst 59 (64.8%) and 53 (58.2%) of the 91 stage-C patients carried *UGT1A7*3* allele and variant-211 *UGT1A1* allele, respectively, and relatively fewer proportion of patients featuring stages A and B bore these two variants [28.0% (49/175) for *UGT1A7*3* allele and 22.8% (40/175) for variant-211 *UGT1A1* allele, respectively]. Compared to the number of CRC patients featuring stages A and B tumors (non-metastases), the OR for developing stages-C and -D CRCs (metastases) for the subjects carrying *UGT1A7*3* allele and variant-211 *UGT1A1* allele was 4.90 ($P<0.001$) and 4.89 ($P<0.001$), respectively. The results of multivariate logistical regressions confirmed that the metastases of CRC was associated with the presence of *UGT1A7*3* allele or variant-211 *UGT1A1* allele (OR = 2.51, $P = 0.01$; and OR = 2.71, $P = 0.01$, respectively), but was independent of age and gender of CRC patients, as shown in Table 7. Table 8 shows that the interaction between the *UGT1A7*3* allele and variant-211 *UGT1A1* allele resulted in an additive effect on the risk of metastases (stages C and D) for CRC patients, as the observed OR (6.83) was greater than the expected OR (4.56) for the development of metastases.

DISCUSSION

Since CRC is a disease of late onset[8], the mean age of our CRC-suffering patient group was relatively greater (mean = 65 years, range 31-92 years) than was the case for the control group (mean = 47 years, range 27-79 years), similar to what was reported for German CRC patients (mean = 63 years, range 38-85 years) and controls (mean = 48 years, range 19-85 years) from a study investigating the relationship between the SNPs of the *UGT1A7* gene and CRC[6]. The association between the SNPs of certain carcinogen metabolizing enzymes and human cancer represents a model combining genetic predisposition and environmental exposure[12]. UGTs are the most important enzymes of phase-II detoxification proteins; therefore, it appears logical that their SNPs are worthy of studies for the development of cancers and evaluation of specific drug therapy regimens for cancer treatment[12]. The study investigating the development of CRC amongst German individuals reported that a highly significant association between the presence of *UGT1A7*3* allele and CRC was observed (OR = 2.75, 95%CI 1.60-4.71)[6]. Contrasting this, however, the results of a study concerning the treatment of Japanese patients with irinotecan, a drug commonly used

Table 1 OR and 95%CI for CRC with *UGT1A7* genotypes and alleles

UGT1A7 genotype or allele	Number (%)		OR (95%CI)	*P*
	Cases ($n = 268$)	Controls ($n = 441$)		
*UGT1A7*1/*1*	76 (28.4)	184 (41.7)	0.55 (0.40–0.77)	<0.001
*UGT1A7*1/*2*	73 (27.2)	117 (26.5)	1.04 (0.74–1.46)	0.84
*UGT1A7*1/*3*	77 (28.7)	75 (17.0)	1.97 (1.37–2.83)	<0.001
*UGT1A7*2/*2*	9 (3.4)	22 (5.0)	0.66 (0.30–1.46)	0.31
*UGT1A7*2/*3*	23 (8.6)	32 (7.3)	1.20 (0.69–2.10)	0.52
*UGT1A7*3/*3*	10 (3.7)	11 (2.5)	1.52 (0.64–3.62)	0.35
*UGT1A7*1*	226 (84.3)	376 (85.3)	1.08 (0.71–1.64)	0.74
*UGT1A7*2*	105 (39.2)	171 (38.8)	1.02 (0.75–1.39)	0.92
*UGT1A7*3*	110 (41.0)	118 (26.8)	1.91 (1.38–2.63)	<0.001

Table 2 The comparisons between the observed percentage with the expected percentage of control subjects carrying *UGT1A7*1/*2*, *UGT1A7*1/*3*, and *UGT1A7*2/*3* genotypes

	Control subjects ($n = 441$)		χ^2	*P*
	Observed percentage (%)	Expected percentage (%)[1]		
UGT1A7*1/*2	26.5	28.9	0.081	0.960
UGT1A7*1/*3	17.0	20.4		
UGT1A7*2/*3	7.3	7.1		

[1]The expected percentage was calculated by the Hardy–Weinberg equilibrium. For example, expected percentage of *UGT1A7*1/*2* = 2× (frequency of *UGT1A7*1/*1*)$^{1/2}$×(frequency of *UGT1A7*2/*2*)$^{1/2}$ = 2×41.7$^{1/2}$×5.0$^{1/2}$ = 28.9%.

Table 3 The comparison of *UGT1A1* genotypes between case and control groups

UGT1A1 genotype	Case group ($n = 268$)		Control group ($n = 441$)		*P* (χ^2 test)
	Number	%	Number	%	
Wild type	121	45.2	218	49.4	0.78
Heterozygous variation	118	44.0	186	42.2[3]	
6/7[1]	37		96		
211 G to A/normal	76		79		
1 091 C to T/normal	5		11		
Compound heterozygous variation	23	8.6	34	7.7	
6/7, 211 G to A/normal	13		6		
6/7, 686 C to A/normal	8		20		
6/7, 1 091 C to T/normal	0		2		
6/7, 211 G to A/normal, 686 C to A/normal	1		2		
6/7, 686 C to A/normal, 1 091 C to T/normal	1		0		
211 G to A/normal, 1 091 C to T/normal	0		4		
Homozygous variation	6	2.2	3	0.7	
7/7[2]	1		0		
211 G to A/211 G to A	4		3		
7/7, 211 G to A/normal	1		0		

[1]6/7 and [2]7/7 represent A(TA)$_6$TAA/A(TA)$_7$TAA and A(TA)$_7$TAA/A(TA)$_7$TAA in the promoter area of *UGT1A1* gene, respectively. [3]The expected frequency is 40.7% calculated by Hardy–Weinberg equilibrium: [2×(frequency of wild type)$^{1/2}$× (frequency of compound heterozygous variation plus frequency of homozygous variation)$^{1/2}$ = 2×49.4$^{1/2}$×(7.7+0.7)$^{1/2}$ = 40.7]. The observed frequency (42.2%) is not significantly different from the expected frequency (40.7%) ($P = 0.89$ by χ^2 test).

Table 4 OR and 95%CI for CRC with *UGT1A1* alleles

UGT1A1 allele	Number (%)		OR (95%CI)	*P*
	Cases ($n = 268$)	Controls ($n = 441$)		
A(TA)$_7$TAA	62 (23.1)	126 (28.6)	0.75 (0.52–1.05)	0.09
Variant-211	95 (35.4)	94 (21.3)	2.03 (1.45–2.84)	<0.001
Variant 686	10 (3.7)	22 (5.0)	0.74 (0.34–1.58)	0.44
Variant 1091	6 (2.2)	17 (3.8)	0.57 (0.22–1.47)	0.25

Table 5 The interaction effect of the *UGT1A7*3* allele and variant-211 *UGT1A1* allele upon the development of CRC

*UGT1A7*3*/ variant-211 *UGT1A1*	Number (%)		OR (95%CI)	*P*
	Cases (*n* = 268)	Controls (*n* = 441)		
Absent/absent	145 (54.1)	302 (68.5)	1.00	
Present/absent	28 (10.4)	45 (10.2)	1.30 (0.78–2.16)	0.39
Absent/present	13 (4.8)	21 (4.8)	1.29 (0.63–2.65)	0.33
Present/present	82 (30.6)	73 (16.5)	2.34 (1.61–3.40)	<0.001
Expected by additive[1]			1.59	

[1]Expected OR under no-interaction additive model.

Table 6 OR and 95%CI of stages-C and -D CRCs with CRC-related *UGT1A* alleles

CRC-related allele	Stage of CRC		OR (95%CI)	*P*
	C and D (*n* = 93)	A and B (*n* = 175)		
*UGT1A7*3*	61[1] (65.6%)	49 (28.0%)	4.90 (2.86–8.41)	<0.001
Variant-211 *UGT1A1*	55[1] (59.1%)	40 (22.9%)	4.89 (2.84–8.41)	<0.001

[1]All the subjects were stage-C patients, except two were stage-D patients.

Table 7 Adjusted odds ratios (AOR) and 95%CI for the different stages of CRC with age, gender, and CRC-related *UGT1A* alleles

Factor	CRC stage		OR (95%CI)	*P*
	C and D (*n* = 93)	A and B (*n* = 175)		
Age >51/≤50 yr	79/14	155/20	0.68 (0.31–1.53)	0.35
Gender male/female	55/38	85/90	1.44 (0.82–2.51)	0.20
*UGT1A7*3*	61 (65.6%)	49 (28.0%)	2.51 (1.23–5.13)	0.01
Variant-211 *UGT1A1*	55 (59.1%)	40 (22.9%)	2.71 (1.31–5.58)	0.01

Table 8 The interaction effect of the *UGT1A7*3* allele and variant-211 *UGT1A1* allele upon the stage of CRC

*UGT1A7*3*/ variant-211 *UGT1A1*	CRC stage		OR (95%CI)	*P*
	C and D (*n* = 93)	A and B (*n* = 175)		
Absent/absent	27 (29.0%)	118 (67.4%)	1.00	
Present/absent	11 (11.8%)	17 (9.7%)	2.83 (1.19–6.72)	0.02
Absent/present	5 (5.4%)	8 (4.6%)	2.73 (0.83–9.01)	0.10
Present/present	50 (53.8%)	32 (18.3%)	6.83 (3.71–12.56)	<0.001
Expected by additive[1]			4.56	

[1]Expected OR under no-interaction additive model.

for the treatment of CRC patients, suggested that the determination of *UGT1A7* genotypes would not be useful for predicting severe toxicity amongst CRC sufferers[13]. On the other hand, the determination of variation in the promoter area of *UGT1A1* gene was found to be clinically useful for predicting the potential for severe toxicity as a consequence of the use of irinotecan amongst Caucasians and Japanese[14-16]. Nevertheless, the *UGT1A1* gene has never been investigated as regarding whether or not it is a risk factor for developing CRC.

In this study, for the first time, the variation of the *UGT1A1* gene was considered to constitute one of the risk factors for causing CRC. It was interesting to find that the variation at nucleotide 211 of the *UGT1A1* gene, the most common variant of the *UGT1A1* gene amongst our populations[3], as well as the presence of the *UGT1A7*3* allele or *UGT1A7*3* allele plus variant-211 *UGT1A1* allele, was involved in the development of CRC. The variant-211 *UGT1A1* gene has been observed to be the key *UGT1A1*-gene defect for the development of neonatal hyperbilirubinemia amongst Asians[10,17-19], as opposed to the homozygous variation in the promoter area, which has been reported to be the responsible region amongst Caucasians[20,21]. In an *in vitro* gene expression study, the UGT1A1 enzyme activities of the 211 A for G substitution for the heterozygous and homozygous state appeared to have reduced to, respectively, 60.2% and 32.2% of normal values[22]. Such decreased enzyme activity is thought, by some, to result in the delayed elimination of bilirubin[22]. We hypothesize that such a functional defect may also occur for the elimination of carcinogen (s), which induces the development of CRC. Another explanation for being a risk factor in the development of CRC is that variant-211 *UGT1A1* allele is associated with *UGT1A7*3* allele. For example, in our previous study, we found that 81 (90.0%) of the 90 subjects featuring the heterozygous G for A substitution at nucleotide 211 of the *UGT1A1* gene and all of the 100 subjects bearing the homozygous G 211 *UGT1A1* gene were carriages of *UGT1A7*3*, respectively. In this current study, a similar result was observed: 73 (77.6%) of the 94 controls and 82 (86.3%) of the 95 CRC patients featuring variant-211 *UGT1A1* alleles were the possessors of *UGT1A7*3* alleles (Table 5). These results indicate that homozygous variation of *UGT1A1* gene at nucleotide 211 and *UGT1A7*3* were in complete linkage disequilibrium, whilst heterozygous variant-211 *UGT1A1* gene was highly associated with *UGT1A7*3* allele. *UGT1A7*3* represents the allele that features the least benzopyrene (a carcinogen)-metabolite glucuronidation activity[6], and therefore it is thought by a number of researchers to be a risk factor for the development of CRC[6,13]. Interestingly, the 211 G to A variation has been found amongst Asians[3,10,17-19], but not for Caucasians[23], suggesting that the clinical significance of the association between variant-211 *UGT1A1* and *UGT1A7*3* alleles is more important for Asian people.

Another novel finding in our study was that the risk for developing metastases amongst the study-participating CRC patients possessing the *UGT1A7*3* allele or variant-211 *UGT1A1* allele was greater than that for those who did not possess these variants. Moreover, an additive interaction effect upon metastases was observed for those patients who featured the *UGT1A7*3* allele plus the variant-211 *UGT1A1* allele. The pathological stage of a tumor upon diagnosis is typically determined by the extent of delay to treatment and the degree of tissue differentiation of certain involved tissue present[9]. Since all of our CRC patients underwent colorectal surgery within 2 mo of initial diagnosis, it would appear unlikely that the delayed tumor treatment for the patients possessing the *UGT1A7*3* allele or variant-211 *UGT1A1* allele would be the reason for causing metastases. Our finding may indicate that the degree of tissue differentiation in the colorectum for CRC sufferers

is more severe, perhaps even as much as is in the development of metastases, amongst individuals who feature the presence of the *UGT1A7*3* allele or variant-211 *UGT1A1* allele than is the case for CRC patients who do not possess those alleles. Clearly, further investigation is warranted in order to evaluate those hypotheses, the results of which should provide useful information for clinical utilization in this realm, because CRC is still currently a life-threatening disease in Taiwan featuring a mortality rate of 16.5 per hundred-thousands[8].

In conclusion, carriage of the *UGT1A7*3* allele, as well as the variant-211 *UGT1A1* allele, is a risk factor for the development of CRC, and also is a determinant of the particular pathological stage of CRC (metastases or not). The risk associating the development and metastases of CRC in the individuals possessing both *UGT1A7*3* and variant-211 *UGT1A1* alleles is higher than those carrying either one of these two variants. The determination of the specific nature of the *UGT1A1* and *UGT1A7* genes may be helpful to improve the chances of prevention of CRC or a reduction in the severity of CRC for certain at-risk groups.

REFERENCES

1 **Radominska-Pandya A,** Czernik PJ, Little JM, Battaglia E, Mackenzie PI. Structural and functional studies of UDP-glucuronosyltransferases. *Drug Metab Rev 1999*; **31**: 817-899
2 **Mackenzie PI,** Owens IS, Burchell B, Bock KW, Bairoch A, Belanger A, Fournel-Gigleux S, Green M, Hum DW, Iyanagi T, Lancet D, Louisot P, Magdalou J, Chowdhury JR, Ritter JK, Schachter H, Tephly TR, Tipton KF, Nebert DW. The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics* 1997; **7**: 255-269
3 **Huang CS,** Luo GA, Huang ML, Yu SC, Yang SS. Variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese. *Pharmacogenetics* 2000; **10**: 539-544
4 **Zheng Z,** Park JY, Guillemette C, Schantz SP, Lazarus P. Tobacco carcinogen-detoxifying enzyme UGT1A7 and its association with orolaryngeal cancer risk. *J Natl Cancer Inst* 2001; **93**: 1411-1418
5 **Vogel A,** Kneip S, Barut A, Ehmer U, Tukey RH, Manns MP, Strassburg CP. Genetic link of hepatocellular carcinoma with polymorphisms of the UDP-glucuronosyltransferase UGT1A7 gene. *Gastroenterology* 2001; **121**: 1136-1144
6 **Strassburg CP,** Vogel A, Kneip S, Tukey RH, Manns MP. Polymorphisms of the human UDP-glucuronosyltransferase (UGT) 1A7 gene in colorectal cancer. *Gut* 2002; **50**: 851-856
7 **Ockenga J,** Vogel A, Teich N, Keim V, Manns MP, Strassburg CP. UDP glucuronosyltransferase (UGT1A7) gene polymorphisms increase the risk of chronic pancreatitis and pancreatic cancer. *Gastroenterology* 2003; **124**: 1802-1808
8 Department of Health, Taiwan. Leading cause of death from cancer, Taiwan area. In: Department of Health, Taiwan, editor. *Health and vital statistics*. Taipei: 2002: 73-77
9 **Lynch HT,** Smyrk TC, Watson P, Lanspa SJ, Lynch JF, Lynch PM, Cavalieri RJ, Boland CR. Genetics, natural history, tumor spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. *Gastroenterology* 1993; **104**: 1535-1549
10 **Huang MJ,** Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. *Pediatr Res* 2004; **56**: 682-689
11 **Hosmer DW,** Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992; **3**: 452-456
12 **Tukey RH,** Strassburg CP. Human UDP-glucuronosyltransferases: metabolism, expression, and disease. *Annu Rev Pharmacol Toxicol* 2000; **40**: 581-616
13 **Ando M,** Ando Y, Sekido Y, Ando M, Shimokata K, Hasegawa Y. Genetic polymorphisms of the UDP-glucuronosyltransferase 1A7 gene and irinotecan toxicity in Japanese cancer patients. *Jpn J Cancer Res* 2002; **93**: 591-597
14 **Ando Y,** Saka H, Asai G, Sugiura S, Shimokata K, Kamataki T. UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. *Ann Oncol* 1998; **9**: 845-847
15 **Iyer L,** Hall D, Das S, Mortell MA, Ramirez J, Kim S, Di Rienzo A, Ratain MJ. Phenotype-genotype correlation of *in vitro* SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with UGT1A1 promoter polymorphism. *Clin Pharmacol Ther* 1999; **65**: 576-582
16 **Ando Y,** Saka H, Ando M, Sawa T, Muro K, Ueoka H, Yokoyama A, Saitoh S, Shimokata K, Hasegawa Y. Polymorphisms of UDP-glucuronosyltransferase gene and irinotecan toxicity: a pharmacogenetic analysis. *Cancer Res* 2000; **60**: 6921-6926
17 **Akaba K,** Kimura T, Sasaki A, Tanabe S, Ikegami T, Hashimoto M, Umeda H, Yoshida H, Umetsu K, Chiba H, Yuasa I, Hayasaka K. Neonatal hyperbilirubinemia and mutation of the bilirubin uridine diphosphate-glucuronosyltransferase gene: a common missense mutation among Japanese, Koreans and Chinese. *Biochem Mol Biol Int* 1998; **46**: 21-26
18 **Huang CS,** Chang PF, Huang MJ, Chen ES, Chen WC. Glucose-6-phosphate dehydrogenase deficiency, the UDP-glucuronosyl transferase 1A1 gene and neonatal hyperbilirubinemia. *Gastroenterology* 2002; **123**: 127-133
19 **Huang CS,** Chang PF, Huang MJ, Chen ES, Hung KL, Tsou KI. Relationship between bilirubin UDP-glucuronosyl transferase 1A1 gene and neonatal hyperbilirubinemia. *Pediatr Res* 2002; **52**: 601-605
20 **Kaplan M,** Renbaum P, Levy-Lahad E, Hammerman C, Lahad A, Beutler E. Gilbert syndrome and glucose-6-phosphate dehydrogenase deficiency: a dose- dependent genetic interaction crucial to neonatal hyperbilirubinemia. *Proc Natl Acad Sci USA* 1997; **94**: 12128-12132
21 **Bancroft JD,** Kreamer B, Gourley GR. Gilbert syndrome accelerates development of neonatal jaundice. *J Pediatr* 1998; **132**: 656-660
22 **Yamamoto K,** Sato H, Fujiyama Y, Doida Y, Bamba T. Contribution of two missense mutations (G71R and Y486D) of the bilirubin UDP glycosyltransferase (UGT1A1) gene to phenotypes of Gilbert's syndrome and Crigler-Najjar syndrome type II. *Biochim Biophys Acta* 1998; **1406**: 267-273
23 **Bosma PJ,** Chowdhury JR, Bakker C, Gantla S, de Boer A, Oostra BA, Lindhout D, Tytgat GN, Jansen PL, Oude Elferink RP. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med* 1995; **333**: 1171-1175

Science Editor Li WZ **Language Editor** Elsevier HK