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

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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.

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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[8]. Two subfamilies, UGT 1 and UGT 2, have been identified in human bodies[9]. 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[10]. 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[11], liver[12], colon[13], and pancreas[14], which are included as leading causes of cancer mortality in Taiwan[15]. 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 Duks 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, EDTA 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 °C, annealing for 60 s at 55 °C, primer extension for 60 s at 72 °C, and a final extension for 10 min at 72 °C. 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 Ava 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, Bfa I, and Acc I 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))-TAA of the 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[10], were run as controls in each performance of genotyping assays by the RFLP method.

**Statistical analysis**

The χ² 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 χ² 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% (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 UGT1A1 allele or variant-211 allele, respectively, and relatively fewer proportion of 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 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 onset⁶, 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 CRC⁹. The association between the SNPs of certain carcinogen metabolizing enzymes and human cancer represents a model combining genetic predisposition and environmental exposure¹². 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 treatment¹². 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)⁹. Contrasting this, however, the results of a study concerning the treatment of Japanese patients with irinotecan, a drug commonly used...

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### Table 1

| UGT1A7 genotype or allele | Number (%) | OR (95%CI) | P |
|---------------------------|------------|------------|---|
| 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

| Control subjects (n = 268) | Expected percentage (%) | χ² | P |
|---------------------------|--------------------------|----|---|
| UGT1A7*1/*2               | 26.5                     | 28.9 | 0.081 | 0.960 |
| UGT1A7*1/*3               | 17.0                     | 20.4 | 0.290 | 0.590 |
| UGT1A7*2/*3               | 7.3                      | 7.1  | 0.005 | 0.940 |

¹The expected percentage was calculated by the Hardy-Weinberg equilibrium. For example, expected percentage of UGT1A7*1/*2 = 2×(frequency of UGT1A7*1)¹×(frequency of UGT1A7*2)¹/2 = 2×(0.20)¹×(0.49)¹/2 = 0.289.

**Table 3**

| UGT1A1 genotype | Case group (n = 268) | Control group (n = 441) | P(χ²test) |
|-----------------|----------------------|-------------------------|-----------|
| Wild type       | 121                  | 218                     | 0.78      |
| Heterozygous variation | 118              | 186                     | 42.2⁶     |
| 6/7⁶             | 37                   | 96                      |           |
| 211 G to A/normal | 76                   | 79                      |           |
| 1091 C to T/normal | 5                    | 11                      |           |
| Compound heterozygous variation | 23              | 34                      | 7.7       |
| 6/7, 211 G to A/normal | 13              | 6                       |           |
| 6/7, 686 C to A/normal | 8                   | 20                      |           |
| 6/7, 1091 C to T/normal | 0                  | 2                       |           |
| 6/7, 211 G to A/normal, | 1                   | 2                       |           |
| 6/7, 686 C to A/normal, | 1                   | 0                       |           |
| 1091 C to T/normal | 0                    | 4                       |           |
| Homozygous variation | 6                    | 3                       | 0.7       |
| 7/7⁶             | 1                    | 0                       |           |
| 211 G to A/211 G to A | 4                   | 3                       |           |
| 7/7, 211 G to A/normal | 1                   | 0                       |           |

⁶/⁷ and 7/7 represent A(TA), TAA/A(TA), TAA and A(TA), TAA/A(TA), TAA in the promoter area of UGT1A1 gene, respectively. The expected frequency is 40.7% calculated by Hardy-Weinberg equilibrium: [2×(frequency of wild type)²×(frequency of compound heterozygous variation plus frequency of homozygous variation)]² = 2×49.4×(7.7+0.7)² = 40.7. The observed frequency (42.2%) is not significantly different from the expected frequency (40.7%) (P = 0.89 by χ²test).

**Table 4**

| UGT1A1 allele | Number (%) | OR (95%CI) | P |
|---------------|------------|------------|---|
| A(TA):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 |
for the treatment of CRC patients, suggested that the determination of UGT1A7 genotypes would not be useful for predicting severe toxicity amongst CRC sufferers[3][9]. 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[10-12]. 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[10-12], as opposed to the homozygous variation in the promoter area, which has been reported to be the responsible region amongst Caucasians[20-22]. 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[23]. Such decreased enzyme activity is thought, by some, to result in the delayed elimination of bilirubin[23]. 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[24], and therefore it is thought by a number of researchers to be a risk factor for the development of CRC[9-12]. Interestingly, the 211 G to A variation has been found amongst Asians[3,10,11,19], 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[25]. 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

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/absent | 82 (30.6) | 73 (16.5) | 2.34 (1.61-3.40) | <0.001 |

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 (65.6%) | 49 (28.0%) | 4.90 (2.86-8.41) | <0.001 |
| Variant-211 | 55 (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 | C and D (n = 93) | A and B (n = 175) | OR (95%CI) | P |
|--------|-----------|-----------------|------------------|------------|---|
| 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 |

1 Expected OR under no-interaction additive model.

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 | Stage of CRC | C and D (n = 93) | A and B (n = 175) | OR (95%CI) | P |
|-------------------------------|--------------|-----------------|------------------|------------|---|
| Absent/absent | 27 (29.0%) | 118 (67.4%) | 1.00 |
| Present/absent | 11 (11.8%) | 19 (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 (3.71-12.58) | <0.001 |

1 Expected OR under no-interaction additive model.
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.

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.

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