*Original Article*

# Polymorphisms of UGT1A7 and XRCC1 are Associated with an Increased Risk of Hepatocellular Carcinoma in Northeast China

Zhi-fang Jia[1], Hong-ying Su[2], Xue-lian Li[1], Xin Xu[1], Zhi-hua Yin[1], Peng Guan[1] Bao-sen Zhou[1*]

[1]*Department of Epidemiology and Key Laboratory of Cancer Etiology and Intervention of Liaoning Province, School of Public Health, China Medical University, Shenyang 110001, China;*
[2]*Department of Intervention, the First Affiliated Hospital, China Medical University, Shenyang 110001, China*

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## ABSTRACT

**Objective:** Hepatocellular carcinoma (HCC) is a complex disease which associates with both environmental and genetic factors. The purpose of this study was to investigate whether the genetic polymorphisms of UDP-glucuronosyltransferase(UGT1A7), an important phase II biotransformation enzyme, and X-ray repair cross-complementing group 1(XRCC1), a pivotal DNA-repair gene, were related to the risk of HCC in Northeast China.

**Methods:** One hundred and thirty six HCC patients and one hundred and thirty six frequency-matched controls were included in this hospital-based case-control study. Genotypes of UGT1A7 and XRCC1 were determined using allele-specific polymerase chain reaction (AS-PCR) and PCR-restriction fragment length polymorphism (RFLP), and for which the odds ratio (OR) with 95% confidence interval (95% CI) were calculated.

**Results:** The proportion of UGT1A7 low enzymatic allele ($^*$2 or $^*$3) was higher in HCC patients than those in controls. The UGT1A7$^*$1/$^*$2 and $^*$3/$^*$3 genotypes were associated with higher HCC risk (OR=2.09, 95%CI: 1.10-3.97; OR=5.67, 95%CI: 1.76-18.30, respectively). The XRCC1 codon 399 Arg/Gln genotype could also elevate HCC risk (OR=2.16, 95% CI 1.29-3.61). In addition to polymorphisms of UGT1A7 and XRCC1, multivariate logistic regression analysis demonstrated that other significant independent factors associated with HCC were HBV infection (OR=68.07, 95%CI: 28.03-165.26), HCV infection (OR=30.97, 95%CI: 8.06-118.94) and family history of HCC (OR=10.62, 95%CI: 2.22-50.77).

**Conclusion:** The study shows that the polymorphisms of UGT1A7 and XRCC1 are associated with HCC risk. Determination of the polymorphisms of UGT1A7 and XRCC1 may provide an important clue to preventive measure against HCC.

**Key words: Hepatocellular carcinoma; (UDP)-glucuronosyltransferase 1A7(UGT1A7); X-ray repair cross-complementing group 1(XRCC1); Risk factors; Genetic polymorphism**

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the third cause of death from cancer in the world. The situation in China is even worse, for about 55% of the world new HCC cases come from China[1] and the incidence rate of HCC in China is increasing[2,3].Chronic infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV), dietary aflatoxin exposure and alcohol consumption are important risk factors for HCC[4]. However, only a minority of people at risk eventually develops HCC and it is likely that there may be some modified mechanisms involved during the development of HCC.

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$^*$Corresponding author.
E-mail: bszhou@mail.cmu.edu.cn

The human uridine 5'-diphosphate (UDP)-glucuronosyltransferases (UGTs) are an enzyme superfamily that catalyzes the glucuronidation of both endogenous compounds such as bilirubin and steroid hormones, as well as exogenous compounds such as environmental carcinogens (including polycyclic aromatic hydrocarbons and heterocyclic amines) and dietary constituents[5,6]. UGT1A7 is one of the products by alternative splicing of exon one to the four common exons(exon2-exon5) of UGT1A gene and it metabolizes a variety of clinically and toxicologically important compounds such as benzo(a) pyrene[7]. So far, several missense variants of UGT1A7 have been discovered at codon 115 (Gly→ Ser), 129(Asn→Lys), 131(Arg→Lys), 139(Glu→Asp), and 208(Trp→Arg) resulting in 11 polymorphic alleles (UGT1A7*1--*11)[8]. Previous study has demonstrated that polymorphisms of codon 129 and 131 are in complete linkage dysequilibrium. Compared to the wild type UGT1A7*1 allele, other variants such as the UGT1A7*2 allele($Lys^{129}Lys^{131}Trp^{208}$) and UGT1A7*3 allele ($Lys^{129}Lys^{131}Arg^{208}$) encode lower catalytic-activity proteins against benzopyrene metabolites[7]. Several studies have suggested a link between polymorphism of UGT1A7 and HCC susceptivity[9-11]. However, the role of the UGT1A7 still needs further study as other studies gained controversial conclusions[12,13].

In addition, DNA repair genes are increasingly studied because of their pivotal role in maintaining genome integrity[14]. The X-ray repair cross-complementing group 1 (XRCC1) functions as a scaffold protein and plays a central role in two interconnected DNA repair pathways: base excision repair (BER) and single-strand break repair (SSBR)[15,16]. Many single nucleotide polymorphisms (SNPs) have been found in XRCC1, and the most extensively studied SNP is Arg399Gln on exon 10. The Arg399Gln allele is situated within the BRCT-1 region harboring the ADPRT binding domain and it has been suggested to be associated with altered DNA repair capacity with an substitution of Arg with Gln[17].

In this study, we detected the genetic polymorphisms of UGT1A7 and XRCC1 genes in a group of hospital-derived HCC patients and their age and gender frequency-matched controls, which all came from Northeast China. This study was a hospital-based, case-control study under an established protocol.

## MATERIALS AND METHODS

### Patients

Blood samples were collected from consecutive HCC patients hospitalizing for the first time in the Department of Intervention, the First Affiliated Hospital of China Medical University from October, 2007 to April, 2008. A total of 136 HCC patients were included who were diagnosed by liver biopsy, or by the findings of radiological features suggestive of HCC in at least two image examinations including abdominal ultrasound, contrast enhanced dynamic computed tomography(CT), magnetic resonance imaging(MRI) and hepatic angiography, or by a single positive imaging technique associated with serum α-fetoprotein level(AFP)>400 μg/L and with no evidence of other tumors. Once recruiting HCC patients, we selected a group of age(±5) and sex frequency-matched controls without clinically apparent liver diseases in the same hospital who attended the physical examination center. Serum hepatitis B surface antigen (HBsAg) and anti-HCV antibody were tested to determine the infection of hepatitis B or hepatitis C by microparticle enzyme immunoassay using commercial assay kits (AxSYM, Abbott, USA). All subjects were investigated with a questionnaire including demographic characteristics, history of disease, consumption of tobacco and alcohol, family history of HCC and other tumors by trained investigators. This study was approved by the Medical Ethical Committee of China Medical University, and informed consent was obtained from all participants.

### Determination of UGT1A7 and XRCC1 Genotype

Blood samples were collected in EDTA tubes and stored at -20°C until DNA extraction. Genome DNA was isolated by potassium iodide technique.

For UGT1A7, as other mutations are rare in humans[18], we screened the mutations in codons 129,131 and 208 using polymerase chain reaction (PCR)-based genotyping techniques including allele-specific PCR (AS-PCR) and PCR-restriction fragment length polymorphism (RFLP) as described[19,20]. Firstly, sequences of UGT1A7 containing codons 129/131 and 208 were amplified using primers UF11 and UR2 (Table 1) to increase specificity as the UGT1A7 gene shared a high level of homology with other UGT related genes. The 25 μl reaction mixture contained 1μl genome DNA, 2μl 10×PCR buffer, 1.6μl each deoxynucleoside triphosphate (dNTPs), 4 pmol each primer and 0.5 units of Taq DNA polymerase (Primers were synthesized by Invitrogen, Beijing, China. Others were obtained from TaKaRa, Dalian, China). The PCR condition was 94°C 7 min followed by 25 cycle of 94°C for 30 s, 56°C for 30 s and 72°C for 40 s and an

ultimate extension at 72°C for 7 min. Secondly, as mutations at codons 129 and 131 were in complete linkage dysequilibrium and closed to each other, allele-specific PCR was applied to determine the sequence variants at codons 129 and 131. Two independent parallel amplifications were performed with different forward primers UF12 and UF13 but the same reverse primer UR2 using the 1000-fold-diluted product of the fist PCR as template. The PCR reaction mixture and condition were similar to the first amplification expect for annealing temperature of 57°C. The products of two pairs of primers were both 454 bp which UF12-UR2 represented existence of the wild haplotype of $Asn^{129}Arg^{131}$ while UF13-UR2 the mutant haplotype of $Lys^{129}Lys^{131}$. Finally, the second PCR products were digested with the restriction enzyme *Rsa* Ⅰ (Invitrogen, Beijing, China) for 2 h at 37°C to detect polymorphism of codon 208. The existence of mutant Arg208 gave two fragments:198 bp and 256 bp, which was not observed in the wild Trp208.

**Table 1.** *Primer sequences for UGT1A7 and XRCC1*

| Genes | Sequence |
|---|---|
| UGT1A7 | |
| UF11 | 5'-TGCCGATGCTCGCTGGACG-3' |
| UF12[a] | 5'-CAAATTGCAGGAGTTTGTTTAATGACCG-3' |
| UF13[b] | 5'-CAAATTGCAGGAGTTTGTTTAAGGACAA-3' |
| UF2 | 5'-CCAATGAAGATCATATTG-3' |
| XRCC1 | |
| XF1 | 5'-TTGTGCTTTCTCTGTGTCCA-3' |
| XR1 | 5'-TCCTCCAGCCTTTTCTGATA-3' |

[a]: Forward primer UF12 was matched with wild haplotype of $Asn^{129}Arg^{131}$, whereas; [b]: Primer UF13 matched with mutant haplotype of $Lys^{129}Lys^{131}$

For XRCC1, PCR-RFLP was carried out to detect the status of codon 399 by primers XF1 and XR1. We undertook PCR using 5 μl genome DNA, 2.5μl 10×PCR buffer, 2μl each deoxynucleoside triphosphate (dNTPs), 5 pmol each primer and 0.6 units of Taq DNA polymerase in a final volume of 25μl. The reaction mixture was denatured at 94°C for 5 min followed by 30 cycles of denatured at 94°C for 30 s, annealing at 57°C for 30 s, elongation at 72°C for 45 s, and a final extension at 72°C for 7 min. The PCR products were then digested with the restriction enzyme *Msp* I. The wild type of Arg399Arg resulted in two fragments: 377bp and 238bp, whereas the homozygote of Gln399Gln only one 615 bp fragment.

All products were separated by electrophoresis on 2% agarose gels and observed on an electrophoresis gel imaging analysis system (Alpha Innotech, USA) with GeneFinder (Bio-Vision, China) staining.

### Statistical Analysis

Categorical variables such as sex, alcohol intake were estimated with Pearson $\chi^2$-test or Fish's exact test. Odds ratios (ORs) with 95% confidence interval (CI) were calculated by logistic regression analysis for allele frequencies and genotype distribution of UGT1A7 and XRCC1. The significant risk factors identified from univariate analysis were evaluated subsequently by the multivariate logistic regression model. A two-tailed *P* value <0.05 was considered to be statistically significant.

## RESULTS

### Characteristics of Subjects

A total of 136 HCC patients and 136 frequency-matched controls were enrolled in this study. Table 2 listed the basic characteristics of the subjects. There were no significant differences between the two groups in distribution of age, gender, cigarette smoking and alcohol intake. However, the HCC patients had significantly higher rates of HBV or HCV infection and family history of HCC than controls (Table 2).

**Table 2.** *Characteristics of subjects*

| Variables | HCC (n=136) No. (%) | Controls (n=136) No. (%) | *P* |
|---|---|---|---|
| Age | | | |
| ≤55 | 58(42.6) | 56(41.2) | |
| 56-65 | 43(31.6) | 42(30.9) | 0.918 |
| >65 | 35(25.7) | 38(27.9) | |
| Sex | | | |
| Male | 112(82.4) | 112(82.4) | 1.000 |
| Female | 24(17.6) | 24(17.6) | |

| | | | |
|---|---|---|---|
| Cigarette smoking | | | |
| Yes | 70(51.5) | 65(47.9) | 0.544 |
| No | 66(48.5) | 71(52.2) | |
| Alcohol intake | | | |
| Yes | 55(40.4) | 43(31.6) | 0.130 |
| No | 81(59.6) | 93(68.4) | |
| HBVinfection[a] | | | |
| Yes | 109(80.1) | 16(11.8) | <0.0001 |
| No | 27(19.9) | 120(88.2) | |
| HCV infection[b] | | | |
| Yes | 18(13.2) | 5(3.7) | 0.005 |
| No | 118(86.8) | 131(96.3) | |
| History of family HCC[c] | | | |
| Yes | 24(17.6) | 5(3.7) | 0.0002 |
| No | 112(82.4) | 131(96.3) | |

OR(95% CI): a, 30.28(15.49-59.20); b, 4.00(1.44-11.10); c, 5.61(2.07-15.20)

**UGT1A7 Polymorphisms and HCC Risk**

UGT1A7 alleles were designated as UGT1A7*1 (wild type, $Asn^{129}Arg^{131}Trp^{208}$), UGT1A7*2 ($Lys^{129}Lys^{131}Trp^{208}$), UGT1A7*3 ($Lys^{129}Lys^{131}Arg^{208}$), UGT1A7*4 ($Asn^{129}Arg^{131}$ $Arg^{208}$) according to the previous study[7]. In this study, we failed to detect any individual carrying the UGT1A7*4 allele. The distributions of UGT1A7 genotypes and alleles were shown in Table 3. The frequencies of UGT1A7*1/*2 and *3/*3 genotypes in HCC patients (36% and 15%) were statistically higher than those in controls (26% and 4%), with ORs of 2.09 (95%CI:1.10-3.97) and 5.67 (95%CI:1.76-18.30) compared with the *1/*1 genotype, respectively. As for the UGT1A7 alleles, we found that both UGT1A7*2 and UGTA7*3 allele could slightly but significantly increase the risk for HCC, with ORs of 1.60 (95%CI:1.03-2.49) and 1.77 (95%CI:1.15-2.74), respectively (Table 3). Furthermore, as previous studies have shown that UGT1A7 isoenzymes encoded by variant UGT1A7 alleles (UGT1A7*2,*3) exhibit lower catalytic activity than that by UGT1A7*1 allele[7], we designated the UGT1A7*1 allele as a higher-activity allele (H allele) and UGT1A7*2,*3 lower-activity alleles (L allele) and categorized UGT1A7 genotype into high (H/H), intermediate (H/L) and low-activity variant (L/L) according to the enzyme activity. When HCC risk was compared with the high catalytic genotype (H/H), significant increase was shown for the intermediate (OR=1.73, 95%CI:1.01-2.96) and the low-activity genotype (OR=2.55, 95%CI:1.28-5.08). An inverse dose-response relationship between the decreased enzymatic activity of UGT1A7 genotype and increased HCC risk was observed (*P*=0.005).

**Table 3.** *Genotype and allele frequencies of UGT1A7 polymorphisms in subjects*

| | HCC (n=136) No.(%) | Controls (n=136) No. (%) | OR(95% CI) | *P* |
|---|---|---|---|---|
| Genotype frequencies | | | | |
| *1/*1 | 41(30.1) | 62(45.6) | 1.00(reference) | — |
| *1/*2 | 36(26.5) | 26(19.1) | 2.09(1.10-3.97) | 0.023 |
| *1/*3 | 27(19.9) | 29(21.3) | 1.41(0.73-2.71) | 0.307 |
| *2/*2 | 8(5.9) | 6(4.4) | 2.02(0.65-6.24) | 0.221 |
| *2/*3 | 9(6.6) | 9(6.6) | 1.51(0.55-4.13) | 0.421 |
| *3/*3 | 15(11.0) | 4(2.9) | 5.67(1.76-18.30) | 0.001 |
| Allele frequencies | | | | |
| *1 | 145(53.3) | 179(65.8) | 1.00(reference) | — |
| *2 | 61(22.4) | 47(17.3) | 1.60(1.03-2.49) | 0.035 |
| *3 | 66(24.3) | 46(16.9) | 1.77(1.15-2.74) | 0.010 |
| Categorized genotype | | | | |
| H/H | 41(30.1) | 62(45.6) | 1.00(reference) | — |
| H/L | 63(46.3) | 55(40.4) | 1.73(1.01-2.96) | 0.043 |
| L/L | 32(23.5) | 19(14.0) | 2.55(1.28-5.08) | 0.007 |

### XRCC1 Polymorphisms and HCC Risk

The distributions of XRCC1 polymorphisms were shown in Table 4. The heterozygous genotype Arg/Gln could slightly increase the risk for HCC (OR=2.16, 95%CI:1.29-3.61). However, this effect was not observed for homozygous Gln/Gln genotype. When considering the allele frequency, the mutant Gln allele statistically increased the HCC risk (OR=1.65, 95%CI: 1.14-2.73).

**Table 4.** *Genotype and allele frequencies of XRCC1 polymorphisms in subjects*

| | HCC(n=136) | Controls (n=136) | OR(95% CI) | *P* |
|---|---|---|---|---|
| Genotype Frequencies | | | | |
| Arg/Arg | 53 | 78 | 1.00(reference) | — |
| Arg/Gln | 66 | 45 | 2.16(1.29-3.61) | 0.003 |
| Gln/Gln | 17 | 13 | 1.93(0.86-4.29) | 0.108 |
| Allele frequencies | | | | |
| Arg | 172 | 201 | 1.65(1.14-2.73) | 0.007 |
| Gln | 100 | 71 | | |

### Multivariate Analysis

We further evaluated factors involved in HCC risk using multivariate logistic regression model (Table 5). In addition to polymorphisms of UGT1A7 and XRCC1, subjects with HBV or HCV infection and family history of HCC incurred significantly higher risks for HCC (OR=68.07, 95%CI:28.03-165.26; OR=30.97, 95%CI:8.06-118.94 and OR=10.62, 95%CI: 2.22-50.77; respectively).

**Table 5.** *Multivariate regression analysis*

| Factors | OR | |
|---|---|---|
| Categorized UGT1A7 genotype | | |
| H/H | 1.00 | — |
| H/L | 2.40 | 1.03-5.64 |
| L/L | 4.56 | 1.42-14.65 |
| XRCC1 | | |
| Arg/Arg | 1.00 | — |
| Arg/Gln | 3.65 | 1.54-8.63 |
| Gln/Gln | 1.69 | 0.45-6.42 |
| HBV infection | 68.07 | 28.03-165.26 |
| HCV infection | 30.97 | 8.06-118.94 |
| Family history of HCC | 10.62 | 2.22-50.77 |

## DISCUSSION

In this study, we examined the polymorphisms of UGT1A7 and XRCC1 in the Northeastern Chinese population with or without HCC. Our study revealed that both UGT1A7 and XRCC1 polymorphisms were independent risk factors of HCC. We also evaluated other factors related to HCC in multivariate model.

UGTs constitute a major cellular defense through its conjugation of hydrophobic compounds both endogenous and exogenous to form water soluble glucuronides which facilitate renal or biliary excretion. Polymorphisms of UGT1A7 could alter the enzymatic activity of the encoded protein[7] and have been reported to be involved in colorectal cancer[20-23], lung cancer[24,25], breast cancer[26], pancreatic cancer[27] and HCC[9,11,28]. Vogel et al[9] first reported that UGT1A7*3 allele could significantly increase HCC risk but Stucker et al[12] found that the association existed only when the case group was restricted to the viral origin. However, Borentain et al [13] failed to find any association between them. In our study, we observed that carriage of UGT1A7*3/*3 or *1*2 genotype was significantly associated with higher HCC risk (OR=5.67, 95%CI:1.76-18.30; OR=2.09, 95%CI:1.10-3.97, respectively) and both UGT1A7*2 and *3 alleles were linked to increased HCC risk (OR=1.60, 95%CI:1.03-2.49; OR=1.77, 95%CI:1.15-2.74, respectively).When we designated the UGT1A7*1 allele as a higher-activity allele (H allele) and UGT1A7*2,*3 as lower-activity allele (L allele) and categorized UGT1A7 genotypes into high (H/H), intermediate (H/L) and low-activity variants (L/L) according to the enzyme activity, an reverse dose-response relationship was found between low-activity genotype and increased risk of HCC (OR=1.73, 95%CI:1.01-2.96; OR=2.55 95%CI: 1.28-5.08, respectively. *P* for trend 0.005). Our results were compatible with previous studies which indicated that polymorphisms of UGT1A7 might be a marker of increased risk for HCC[9-11, 28].

Recent studies suggested that the polymorphism of DNA repair gene XRCC1 at codon 399 with a substitution of glutamine (Gln) for arginine (Arg) could alter the activity of DNA repair and was associated with risk of various cancers[29-32]. Yu et

al[33] did not observe an independent increase in HCC risk of Gln allele although a trend was present. However, Kirk et al [34] observed a 3-fold increased risk of HCC in patients with heterozygote genotype (Arg/Gln).Our study found a similar result that Arg/Gln genotype was significantly associated with HCC (OR=2.16, 95%CI:1.29-3.61).The variant allele Gln could slightly increase the HCC risk (OR=1.65, 95CI:1.14-2.73). However, we could not observe a statistical association of the homogeneous of Gln/Gln which might due to the low sample size.

As HCC was considered to be a multifactorial disease, we further performed multivariate logistic regression analysis to evaluate HCC risk. Besides the polymorphisms of UGT1A7 and XRCC1, HBV infection, HCV infection and family history of HCC also entered into the multivariate model. This result confirms the multifactorial characteristics of hepatocarcinogenesis. In addition to the environmental factors such as virus infection, genetic predisposition to HCC deserves to be paid enough attention.

As far as we know, this was the first study to examine the UGT1A7 polymorphisms in HCC patients coming from Chinese mainland. However, we are aware that there may be potential limitation in our study. We could not evaluate the roles of gender and age which have been suggested to be associated with HCC risk because of the frequency-matched cases and controls by gender and age. However, the gender ratio (male:female) in HCC group was 4.7:1, which may indicate that HCC was more prevalent in male gender as we selected patients consecutively.

In summary, polymorphisms of UGT1A7 and XRCC1 are independently associated with HCC risk in addition to HBV or HCV infection and family history of HCC. The UGT1A7 *2 or *3 allele as well as XRCC1 Gln allele at codon 399 might be used as markers related to higher risk of HCC.

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