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RESEARCH

Association of Genetic Polymorphisms in *HSD17B1*, *HSD17B2* and *SHBG* Genes with Hepatocellular Carcinoma Risk

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Abstract Genetic polymorphisms of enzymes involved in estrogen synthesizing/transporting can influence the risk of hormone-dependent diseases. The incidence rate and relative risk for hepatocellular carcinoma (HCC) are higher in men than in women. This study was conducted to explore the relationship of single nucleotide polymorphisms (SNPs) in 17 β-Hydroxysteroid dehydrogenases (*HSD17B1* and *HSD17B2*) and sex hormone-binding globulin (*SHBG*) genes with the risk of HCC within Chinese Han population. Polymorphisms of *HSD17B1* rs676387, *HSD17B2* rs8191246 and *SHBG* rs6259 were genotyped in 253 HCC patients and 438 healthy control subjects using the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP). Significantly increased HCC risk was found to be associated with T allele of rs676387 and G allele of rs8191246. Increased HCC risks were found in different genetic model (TT genotype in a recessive model, T allele carriers in a dominant model, TT genotype and TG genotype in a codominant model for *HSD17B1* rs676387, G allele carriers in a dominant model and AG genotype in a codominant model for *HSD17B2* rs8191246, respectively). No association between *SHBG* rs6259 and HCC risk was observed. The present study provided evidence that *HSD17B1* rs676387 and *HSD17B2* rs8191246 were association with HCC development. Further studies in diverse ethnic population with larger sample size were recommended to confirm the findings.

Keywords *SHBG* · *HSD17B1* · *HSD17B2* · HCC

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Introduction

Hepatocellular carcinoma (HCC) causes about half a million deaths every year and ranks the fifth common types of cancers worldwide [1, 2]. Epidemiologic studies found that HCC presents a prominent male dominance, with a male: female ratio range of 1.5–11:1 in different series of analyses [1]. HCC is usually caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infections or by alcoholic/metabolic etiologies [3, 4]. Male has also been considered to be a major risk factor of HCC [3, 4]. Epidemiological and experimental evidence further pointed out that sex steroid hormones including androgen and estrogen might function as major regulatory factors, which can influence susceptibility to disease and to neoplastic transformation [5]. Long-term use of oral contraceptives and

anabolic androgenic steroids can induce HCC [6]. Animal models also showed a relationship between exposition to sex hormones and HCC development, suggesting that hormones might play a role as inducer and promoter in the process of liver carcinogenesis [5].

17 β-Hydroxysteroid dehydrogenases (17HSD) family, including phase I- and II-metabolizing enzyme, affects the availability of active oestrogens [7]. 17HSD type 1 catalyses reduction of oestrone to oestradiol with NADP(H) as a cofactor, and 17HSD type 2 catalyses oxidation from oestradiol to oestrone with NAD(H) as a cofactor [8]. The *HSD17B1* locates in chromosome 17q12 and has a polymorphic site (rs676387, G/T). The *HSD17B2* locates in chromosome 16q24.1 and has a nonsynonymous mutation (rs8191246, A/G, Ter388Trp) in the coding regions. Polymorphisms in estrogen-metabolizing genes may potentially cause alterations in their biological function and thus contribute to the susceptibility of an individual to hormone-related cancers [9].

The human *SHBG* gene is located on the short arm (17p12 → p13) of chromosome 17 [10]. SHBG carries the estrogens to the target tissue and act as a sex hormone transporter [11, 12]. In addition, previous reports indicated that SHBG might be an active regulator of the steroid-signaling system in target tissues [13, 14]. Recent studies found an SNP site (rs6259, A/G) at nucleotide 5,790 in exon 8 of *SHBG*, resulting in an amino acid substitution of asparagine for aspartic acid at residue 327 (Asp327Asn) in the *SHBG* polypeptide [10]. In the past years, numerous genetic association studies have explored the role of *SHBG* rs6259 polymorphisms in several kinds of cancers, including breast cancer [15], endometrial cancer [16], ovarian cancer [17] and prostate cancer [18].

Based on the previous findings, we hypothesized that genetic variations in sex hormone synthesizing enzymes (*HSD17B1*, *HSD17B2*) and sex hormone transporter (*SHBG*), may influence the risk of HCC development. Therefore, we evaluated the association of three selected SNPs (rs676387 in *HSD17B1* gene, rs8191246 in *HSD17B2* gene and rs6259 in *SHBG* gene) with HCC risk in a case–control study of the Chinese Han population.

Materials and Methods

Study Subjects

In this study, 253 patients with HCC were selected consecutively from the West China Hospital of Sichuan University between June 2008 and October 2010. This cohort of patients had been diagnosed, pathologically confirmed, and untreated before the blood samples were taken. Clinical characteristics was abstracted from the participants' medical records regarding the individual's gender, age, family history of HCC, and the state of hepatitis B surface antigen (HBs Ag) which indicates whether to be infected by HBV or not. The control group was recruited from a routine health survey with a total number of 438 unrelated individuals, and inclusive criteria for controls were no evidence of any personal or family history of cancer or other serious diseases or hepatitis virus infection. The demographics of the patients and controls enrolled in this study were shown in Table 1. This study was performed with the approval of the ethics committee of Sichuan University and all the participants provided the written informed consent.

Genotyping

Genomic DNA was extracted from peripheral blood using a blood DNA isolation kit (Bioteke Inc., China). The genotypes of *HSD17B1* rs676387 gene, *HSD17B2* rs8191246 gene and *SHBG* rs6259 gene were determined using PCR–RFLP. The sequence of primers and condition for amplification were according to the previously published [19, 20]. Amplification products were digested by HinfI for rs6259, BclI for rs676387 and StyI for rs8191246, respectively [19, 20]. PCR and digestion products were analyzed directly by vertical nondenaturing polyacrylamide gel electrophoresis and visualized by silver staining. To confirm the accuracy of the method, we selected 10 % of the samples for repeated experiments and the results were 100 % concordant.

Statistical Analysis

The data analysis was carried out by using SPSS 17.0 (SPSS Inc., Chicago, IL) statistical software. Hardy–Weinberg equilibrium was tested with a goodness of fit chi-square test to compare the observed genotype frequencies among the control subjects. Genotype and allele frequencies of the genes were compared between HCC patients and control subjects by the chi-square test. Genotypic association tests in a case–control pattern assuming codominant, dominant and recessive genetic models were performed. Odds ratios (ORs) corresponding to 95 % confidence intervals (CIs) were used to evaluate the relative risk conferred by a particular allele or genotype. $P<0.05$ was considered statistically significant.

Results

The genotypes and allele frequencies of three SNPs (*HSD17B1* rs676387, *HSD17B2* rs8191246 and *SHBG* rs6259) in all subjects are shown in Tables 2 and 3. All the genotypes in the control group were in agreement with the Hardy–Weinberg equilibrium. As shown in Table 2, significantly increased HCC risk was found to be

Table 1 Clinical characteristics of the HCC patients and controls

Characteristics	HCC patients *n*=253 (%)	Controls *n*=438 (%)	OR(95 % CI)	X^2-value	*P*
Gender					
Male	220 (87.7)	364 (83.1)	1		
Female	31 (12.3)	74 (16.9)	0.69(0.44-1.09)	2.55	0.11
Age (years)					
Mean ± SD	51.8±12.7	48.2±15.8			
HBV serological markers					
HBs Ag(+)	196				
HBs Ag(−)	57				

n: the number of individuals

associated with T allele of rs676387 and G allele of rs8191246 (*P*=0.001, OR=1.45, 95 % CI: 1.15–1.82, and *P*=0.007, OR=1.65, 95 % CI: 1.14–2.39, respectively). However, no statistically significant difference was observed for *SHBG* rs6259. As shown in Table 3. For *HSD17B1* rs676387, significantly increased HCC risk was found to be associated with the T allele carriers in a dominant model (GT/TT vs. GG, *P*=0.006, OR=1.57, 95 % CI: 1.14–2.17), TT genotype in a recessive model (TT vs. GG/GT, *P*=0.01, OR=1.86, 95 % CI: 1.15–3.00), GT genotype and TT genotype in a codominant model (GT vs. GG, *P*=0.033, OR=1.44, 95 % CI: 1.03–2.02; TT vs. GG, *P*=0.002, OR=2.28, 95 % CI: 1.36–3.83). For *HSD17B2* rs8191246, a significantly increased HCC risk was observed to be associated with G allele carriers in a dominant model (GG/AG vs. AA, *P*=0.012, OR=1.66, 95 % CI: 1.12–2.47) and AG genotype in a codominant model (AG vs. AA, *P*=0.024, OR=1.59, 95 % CI: 1.06–2.39). However, for SHBG rs6259, no statistically significant difference was detected between HCC patients and controls.

The study power has been performed with the Quanto 1.1.1 software. Under a dominant genetic model, at the 0.05 level of significance with the two-sided test for these two polymorphisms, our study had 94.94 %, 82.7 % and 91.21 % power (for *HSD17B1* rs676387, and *HSD17B2* rs8191246 and *SHBG* rs6259) to detect an effect with a relative risk of 1.8 in the group of HCC patients and healthy controls.

Discussion

In humans, exogenous administration of androgenic steroids and estro-progestinics can affect HCC risk [21, 22]. Considering the function of estrogen, this study assessed the gender-specific disease association of genetic variants within the hormone metabolism-related gene (*HSD17B1* rs676387, *HSD17B2* rs8191246) and sex steroid hormone transporter (*SHBG* rs6259) in Chinese Han population. In this study, we found that T allele, T allele carriers in a dominant model, TT genotype in a recessive model as well as GT genotype and TT genotype in a codominant model of rs676387 were associated with increasing HCC risk. Moreover, G allele, G allele carriers in a dominant model and AG genotype in a codominant model of *HSD17B2* rs8191246 were found to be increased HCC risk. However, no association between *SHBG* rs6259 polymorphism and HCC risk was found out.

Hydroxysteroid dehydrogenase 17B (HSD17B) are involved in the synthesis and metabolism of sex steroid hormones. There are at least 11 human HSD17b isoenzymes expression in a variety of tissues such as liver, ovary, placenta, uterus, adipose tissue prostate and testis [23]. HSD17B1 enzyme catalyzing the conversion from estrone into estradiol, and catalyzes the final step of estradiol biosynthesis. HSD17B1 is expressed in the ovaries, placenta, testis, endometrium, malignant, normal breast epithelium and prostatic cancer cells [24, 25]. Recently, many studies have focused on

Table 2 *HSD17B1*, *HSD17B2* and *SHBG* alleles of the HCC patients and controls

Gene	Allele	HCC patients *n*=253 (%)	Controls *n*=438 (%)	OR (95 % CI)	X^2	*P*
HSD17B1	G	300 (59.3)	594	1.00 (reference)		
rs676387	T	206 (40.7)	282 (32.2)	1.45 (1.15–1.82)	10.2	**0.001**
HSD17B2	A	446 (88.1)	810 (92.5)	1.00 (reference)		
rs8191246	G	60 (11.9)	66 (7.5)	1.65 (1.14–2.39)	7.24	**0.007**
SHBG	A	58 (11.5)	106 (12.1)	1.00 (reference)		
rs6259	G	448 (88.5)	770 (87.9)	1.06 (0.76–1.50)	0.13	0.724

n: corresponds to the number of individuals. Boldfaced values indicate a significant difference at the 5 % level

Table 3 *HSD17B1*, *HSD17B2* and *SHBG* genotypes of the HCC patients and controls

Genetic model	Genotype	HCC patients n=253 (%)	Controls n=438 (%)	OR (95 % CI)	X^2	P
HSD17B1 rs676387 G/T						
Codominant	GG	85 (33.6)	194 (44.3)	1.00 (reference)		
	GT	130 (51.4)	206 (47.0)	1.44 (1.03–2.02)	4.54	**0.033**
	TT	38 (15.0)	38 (8.7)	2.28 (1.36–3.83)	10.01	**0.002**
Dominant	GG	85 (33.6)	194 (44.3)	1.00 (reference)		
	GT/TT	168 (66.4)	244 (55.7)	1.57 (1.14–2.17)	7.62	**0.006**
Recessive	GG/GT	215 (85.0)	400 (91.3)	1.00 (reference)		
	TT	38 (15.0)	38 (8.7)	1.86 (1.15–3.00)	6.59	**0.01**
HSD17B2 rs8191246 A/G						
Codominant	AA	197 (77.9)	374 (85.4)	1.00 (reference)		
	AG	52 (20.6)	62 (14.2)	1.59 (1.06–2.39)	5.07	**0.024**
	GG	4 (1.5)	2 (0.4)	3.80 (0.69–20.91)	2.71	0.1
Dominant	AA	197 (77.9)	374 (85.4)	1.00 (reference)		
	AG/GG	56 (22.1)	64 (14.6)	1.66 (1.12–2.47)	6.32	**0.012**
Recessive	AA/AG	249 (98.5)	436 (99.6)	1.00 (reference)		
	GG	4 (1.5)	2 (0.4)	3.50 (0.64–19.26)	2.34	0.125
SHBG rs6259 A/G						
Codominant	AA	3 (1.2)	10 (2.3)	1.00 (reference)		
	AG	52 (20.6)	86 (19.6)	2.02 (0.53–7.67)	1.09	0.296
	GG	198 (78.2)	342 (78.1)	1.93 (0.53–7.10)	1.01	0.31
Dominant	GG	198 (78.2)	342 (78.1)	1.00 (reference)		
	AG/AA	55 (21.8)	96 (21.9)	0.99 (0.68–1.44)	0.003	0.956
Recessive	AG/GG	250 (98.8)	428 (97.7)	1.00 (reference)		
	AA	3 (1.2)	10 (2.3)	0.51 (0.14–1.88)	1.05	0.306

n corresponds to the number of individuals

Boldfaced values indicate a significant difference at the 5 % level

the *HSD17B1* rs676387 polymorphism with susceptibility of disease association with hormone. Feigelson et al. [26] surveyed the *HSD17B1* rs676387 and the risk of breast cancer base on 5,370 breast cancer cases and 7,480 matched controls. They did not find any evidence of correlation between *HSD17B1* haplotypes and breast cancer. Kraft et al. [27] found no evidence of relevance between prostate cancer and common variants in *HSD17B1*, after comprehensively screening *HSD17B1* for variation in U.S. and European whites with a total of 17,657 subjects. When stratified analysis by ethnicity, they found CAGC haplotype had a significant inverse association with risk of prostate cancer in Latinos and Japanese Americans. And they considered the source of conflict results might due to sample size and the ethnicity heterogeneity. Cong et al. [19] genotyped 121 patients with uterine leiomyoma and 217 healthy control in a Chinese population, and found no association between *HSD17B1* rs676387 polymorphism with uterine leiomyoma. In the present study, we found that *HSD17B1* rs676387 could influence susceptibility to HCC. Our results were inconsistent with most of the case–control hormone-related cancers studies [19, 26–28]. The differences might be due to the different type of cancer and discrepant genetic composition between these ethnic populations. Thus, additional data from diverse ethnic group studies are needed to clarify our findings. HSD17B2 is responsible for the inactivation of estradiol into estrone [29]. HSD17B2 isoenzyme has been shown to inactivate sex steroids in the liver, placenta and endometrium [30, 31]. Our study found that *HSD17B2* rs8191246 may act as an important role in HCC development. The result was consistent with the previous reports, which investigated the *HSD17B2* gene polymorphism in prostate cancer [32] and spermatogenic defect [33].

During the last few years, several studies were undertaken to investigate the association between *SHBG* rs6259 polymorphism with the hormone sensitive cancers. In a large case–control study of Chinese postmenopausal women, *SHBG* rs6259 A allele was significantly associated with a reduced risk of breast cancer by increasing serum SHBG levels [15]. Whereas, there was not any association between the A allele and breast cancer risk in Polish, Nordic and U.K. populations [34, 35]. Similarly, A allele was associated with a reduced endometrial cancer risk only in postmenopausal women but

not in premenopausal women [16]. In addition, heterozygote of *SHBG* rs6259 was found to increase the risk of developing prostate cancer [18]. However, Cunningham et al. [36] found no difference in the distribution of the *SHBG* rs6259 polymorphism between prostate cancer patients and healthy controls. Furthermore, although ovarian cancer patients were found to have less frequent of the A allele compared to controls, the difference was not statistically significant [17]. In the present study, distribution of the *SHBG* rs6259 genotypes in HCC patient were similar to the controls, and the data implied that *SHBG* rs6259 polymorphism may not increase risk in HCC development. This result was consistent with the former studies in breast cancer [34, 35, 37], prostate cancer [36] and ovarian cancer [17].

In summary, to our knowledge, this is the first report which explored the polymorphism of *HSD17B1* rs676387, *HSD17B2* rs8191246 and *SHBG* rs6259 with risk of HCC in southwest Chinese Han population. *HSD17B1* rs676387 and *HSD17B2* rs8191246 were observed to be associated with the risk for HCC, indicating that they may participate in the development and progression of HCC. Larger sample size and diverse ethnic groups studies are needed to clarify the findings in the future.

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Conflict of Interest The authors have declared that no conflict of interest exists.

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