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ORIGINAL ARTICLE

TNIP1 Polymorphisms with the Risk of Hepatocellular Carcinoma Based on Chronic Hepatitis B Infection in Chinese Han Population

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Abstract

Chronic hepatitis B virus (HBV) infection is an important etiology for the development of hepatocellular carcinoma (HCC). Tumor necrosis factor-α-induced protein 3-interacting protein 1 (*TNIP1*) is linked to specific inflammatory diseases as a novel type of endogenous inflammatory regulator. However, presently, rare information is found about the association between *TNIP1* polymorphisms and HBV-induced HCC risk. In this case control study, we genotyped four single nucleotide polymorphisms (SNPs) in *TNIP1* gene in 248 HCC patients and 242 chronic HBV carriers using Sequenom Mass-ARRAY technology. Genetic model and haplotype analysis were performed to evaluate the association between candidate SNPs polymorphisms and HBV-induced HCC susceptibility using Pearson's χ^2 test and unconditional logistic regression analysis. Overall, we found two risk alleles in *TNIP1* for HBV-induced HCC in patients: the allele "G" of rs7708392 by genotype model ("G/C" vs. "C/C": OR 1.88, 95% CI 1.17–3, $P=0.009$) and dominant model ("G/C-G/G" vs. "C/C": OR 1.69, 95% CI 1.08–2.65, $P=0.023$), and the allele "C" of rs10036748 by genotype model ("C/T" vs. "T/T": OR 1.83, 95% CI 1.14–2.92, $P=0.012$) and dominant model ("C/T-C/C" vs. "T/T": OR 1.65, 95% CI 1.05–2.59, $P=0.03$). However, rs3792792 and rs4958881 polymorphisms didn't significantly correlate with the risk of HBV-induced HCC. Haplotype analysis showed no significant association between haplotypes and the HCC risk in HBV carriers. This study provides evidence for HBV-induced HCC susceptibility gene *TNIP1* in the Chinese Han population.

Keywords Hepatocellular carcinoma (HCC), hepatitis B virus (HBV) · Tumor necrosis factor-α-induced protein 3-interacting protein 1 (TNIP1) · Association study

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Abbreviations

ORs	Odds ratios
CI	Confidence interval
SNP	Single nucleotide polymorphism
HWE	Hardy–Weinberg equilibrium
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
GWAS	Genome-wide association studies
MAF	Minor allele frequency

Introduction

According to the registration data of China National Central Cancer Registry in 2013, liver cancer was the third most common cancers of incidence, accounting for about 9.84% of all new cancers, and liver cancer also was the common cause of death, accounting for about 14.17% of all cancer deaths (Chen et al. 2013). Hepatocellular carcinoa (HCC) is the most frequency subtype of primary liver cancer accounting for between 70 and 85%. Chronic hepatitis B virus (HBV) infection is responsible for 60% of HCCs, especially in East, the middle zone of Eastern Asia and in sub-Saharan Africa (Iavarone and Colombo 2013; Perz et al. 2006). It has been widely accepted that multiple genetic factors play a crucial role in the development of HBV-induced HCC.

Single nucleotide polymorphism (SNP) refers to a single-nucleotide substitution of one base into another in DNA sequences (Madsen et al. 2007). In recent years, several genome-wide association studies (GWAS) and Meta-analysis have linked some variety of genetic abnormality in the risk of HBV-induced HCC (Li et al. 2018; Tian et al. 2017). Rs7574865 at *STAT4* gene and rs9275319 at *HLA-DQ* gene (Jiang et al. 2013), rs17401966 at *KIF1B* gene (Zhang et al. 2010), rs2288563 and rs2562832 at *TTN* (Yang et al. 2017) loci polymorphisms were found significantly associated with the susceptibility of HBV-induced HCC. Additionally, inflammatory cytokines also have effect on the development of HCC in chronic HBV carriers. Rs2275913 on *IL-17A* (Li et al. 2014), rs2596542 on *MICA* (Kumar et al. 2012), and rs187238 on IL-18 (Dai et al. 2017) loci variants were identified associated with the risk of HBV-related liver diseases. These findings remind us that polymorphisms of genes involving inflammation may provide us a better understanding of HBV-induced HCC.

Tumor necrosis factor-α-induced protein 3-interacting protein 1 (*TNIP1*), located on chromosome 5q32-33.1, is known as A20 binding inhibitors of nuclear factor-κβ (NF-κβ) (Fukushi et al. 1999). It has been demonstrated that TNIP1 as a novel type of endogenous inflammatory regulator is linked to specific inflammatory diseases (Ramirez et al. 2012), and involve in maintaining the homeostasis of immune system (Ramirez et al. 2015; Zhang et al. 2012). It is fascinating to note intracellular immune factors were relevant to the HCC risk in HBV carriers. Nevertheless, the connection between polymorphisms of *TNIP1* gene and the susceptibility of HBV-induced HCC is poorly understood. Herein, a case–control study was performed to explore the association between TNIP1 polymorphisms and the susceptibility of HCC in chronic HBV carriers.

Materials and Methods

Study Participants

Totally, 490 Chinese Han subjects were recruited from the Haikou People's Hospital, among them the case group consisted of 248 HCC patients, and the control group consisted of 242 chronic HBV carriers. HCC patients were diagnosed with dynamic contrast enhanced nuclear magnetic resonance imaging and/or biopsy test (Bruix and Sherman 2011). Cases and controls were all positive for Hepatitis B surface antigen and antibody to hepatitis B core antigen test. To reduce the potential environmental and therapeutic factors impacting the variation of complex human diseases, we have developed a detailed exclusion and screening criteria. Each subject must be ethnic Han Chinese from Hainan provinces, where their ancestors lived for at least three generations. All participates receiving radiotherapy or chemotherapy were excluded, and patients with previous history of other autoimmune disease, family history of genetic cancer, surgical contraindication, pregnancy, active liver disease, or poor compliance were also excluded.

Clinical Data and Demographic/Ethics Statement

All data of individual subjects were obtained from case records including sex, age, smoking status, and drinking status. All subjects have perceived and provided their written information and consent form for this study. Our experiment strictly followed the principle of the declaration of Helsinki expressed. The Human Research Committee for Approval of Research Involving Human Subjects, first People's Hospital of Yunnan Province and Haikou People's Hospital, approved the use of human blood samples in this study.

DNA Extraction

Peripheral blood was collected from both cases and controls for DNA extraction, and the blood samples were stored in − 80 °C refrigerator until use. We followed the manufacturer's instructions using the GoldMag-mini full-blood genomic DNA purification kit to extract genomic DNA from peripheral blood leukocytes in all blood samples (GoldMag. Co. Ltd., Xi'an, China). Spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, USA) was used to measure the concentration and purity of DNA.

SNP Selection and Genotyping

In this experiment, SNPs in the TNIP1 gene were selected from DbSNP database (http://www.hapmap.org/index.html.en) and SNP Consortium database (http://snp.cshl.org/). Moreover, candidate SNPs in TNIP1 gene were selected from previously established polymorphisms associated with other diseases (Li et al. 2017; Song et al. 2017). Validated SNPs were selected with a minor allele frequency > 5% in the HapMap Chinese Han Beijing. Finally, a total of four SNPs (rs3792792, rs4958881, rs7708392 ,and rs10036748) were selected for further genotyping.

Sequenom Mass-ARRAY Assay Design 3.0 Software was used to design a single base extension primer, and according to the manufacturer's protocol, Genotyping was performed on the Sequenom Mass-ARRAY RS1000 platform (Trembizki et al. 2014). The PCR primers for each SNP are shown in Table 1. Data management and analysis were performed using the Sequenom Typer 4.0 Software (Thomas et al. 2007).

Statistical Analysis

Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and the SPSS 18.0 statistical package (SPSS, Chicago, IL, USA) were used to perform statistical analyses. Differences in the characteristics of the case and control study populations were analyzed using χ^2 tests for categorical variables and Welch's t tests for continuous variables. The control group needed to detect whether the Hardy–Weinberg equilibrium (HWE) met, and exact test was used to determine the SNPs departed from the HWE. In this study, the lower frequency allele was considered to be the 'risk' allele. Four genotype models (co-dominant, dominant, recessive, and additive) were used to assess the association between each genotype and the susceptibility of HBV-related HCC. SHEsis software platform and Haploview software package (version 4.2) (Broad Institute, Cambridge, MA, USA) were used to construct the linkage disequilibrium block (Barrett et al. 2005; Li et al. 2009). Pearson's χ^2 tests and unconditional logistic regression analysis adjusted by age, sex, smoking, and drinking status was used to evaluate odds ratio (OR) and 95% confidence interval (CI). All statistical tests were two-sided, and $P = 0.05$ was considered the threshold of whether statistical significance was achieved or not.

Results

We are showing the characteristics of all the participants in Table 2. The experiment involved 248 cases (192 males and 56 females) and 242 controls (188 males and 54 females), and the gender distribution between two groups was matched ($P = 0.944$). The average ages of cases and controls were 54.47 ± 12.05 and 50.04 ± 12.05 years severally. The age distribution was found have an evident difference ($P < 0.001$). The smoking status and drinking status were also investigated, but some subjects

Table 1 Primers

SNP#	2st_PCR primer	1st_PCR primer	UEP-SEQ
rs3792792	ACGTTGGATGATGGCAGCTGTTACGGCCAC	ACGTTGGATGCTCAGATCAGTTCACTCCTC	ccctTTACGGCCACCACCAAGCATG
rs4958881	ACGTTGGATGTGCAATTCCACCCAAGGATG	ACGTTGGATGCACAAATATGTGGACAGTTT	GGATGAAAGGAAGTGAGA
rs7708392	ACGTTGGATGGGGTCTCTTCTGGAACTTAG	ACGTTGGATGAGGCCAACTGGTCAATTCTC	ggggaTGGAACTTAGTAGACTAGTCA
rs10036748	ACGTTGGATGCTTTCATAGCATGATACACG	ACGTTGGATGGCAAAGCAGCCCCTTTTTTC	ACGTATGAGAAAAATAAAATAGTAA

UEP_SEQ unextended mini-sequencing primer

Table 2 Distributions of select variables in liver cancer patients and hepatitis B patients

Variables	Case	Control	*P* value
Gender			0.944^a
Male (%)	192 (77.4%)	188 (77.7%)	
Female (%)	56 (22.6%)	54 (22.3%)	
Age (year)			
Mean age ± SD	54.47 ± 12.05	50.04 ± 12.05	$<0.001^b$
Smoking status			
Non-smoker (%)	156 (62.9%)	116 (47.9%)	$<0.001^a$
Smoker (%)	43 (17.3%)	126 (52.1%)	
Missing (%)	49 (19.8%)		
Drinking status			
Non-drinker (%)	160 (64.5%)	152 (62.8%)	$<0.001^a$
Drinker (%)	26 (10.5%)	90 (37.2%)	
Missing (%)	62 (25%)		

P^a value was calculated by Pearson's χ^2 test

P^b value was calculated by Student's *t* test

were not clear. Therefore, the method of unconditional logistic regression analysis adjusted by gender, age, smoking, and drinking was used for the following data analysis.

The call rates of all SNP were above 95%. Chromosomal position, minor allele and major allele, P^{HWE} value and minor allele frequency of every candidate SNPs are presented in Table 3. There were four SNPs rs3792792, rs4958881, rs7708392, and rs10036748, among them only rs4958881 had an obvious deviation from HWE ($P<0.001$). As for the other three SNPs, they were in HWE in the controls ($P>0.05$). Rs4958881 was excluded from subsequent analysis.

In Table 4, genotype model were constructed to assess the association between SNP variants and HBV-induced HCC risk. Compared with the "C/C" genotype, the "G/C" genotype frequency of rs7708392 polymorphisms among cases was significantly different from controls ("G/C" vs. "C/C": OR 1.88, 95% CI 1.17–3,

Table 3 Basic infromation of candidate SNPs and allele frequencies in case and control

SNP rs#	Chromosome	Position	Band	Alleles A/B	Gene	Role	P-^{HWE}	Minor allele frequency	
								Case	Control
rs3792792	5	150440506	5q33.1	C/T	TNIP1	Intron	1	0.091	0.066
rs4958881	5	150450236	5q33.1	C/T	TNIP1	Intron	<0.001	0.091	0.068
rs7708392	5	150457485	5q33.1	G/C	TNIP1	Intron	0.8612	0.241	0.225
rs10036748	5	150458146	5q33.1	C/T	TNIP1	Intron	0.8612	0.241	0.227

SNPs single nucleotide polymorphisms, *A* miner alleles, *B* major alleles, *HWE* Hardy–Weinberg equilibrium, *OR* odds ratio, *CI* confidence interval

P-^{HWE} value was calculated by exact test

Table 4 Association between polymorphism of candidate SNPs and the HBV-related HCC risk under genetic models

SNP rs#	Allele A/B	Model	Genotypes	Genotype frequency		With adjustment	
				Case	Control	OR (95% CI)	P^a
rs3792792	C/T	Co-dominant	T/T	82.26%	86.89%	1	–
			C/T	17.34%	13.11%	–	–
			C/C	0.4%	0%	–	–
		Dominant	T/T	82.26%	86.89%	0.88 (0.48–1.61)	0.678
			C/T-C/C	17.74%	13.11%		
		Recessive	T/T-C/T	99.6%	100%	–	–
			C/C	0.4%	0%		
		Additive	–	–	–	0.88 (0.48–1.61)	0.678
rs7708392	G/C	Co-dominant	C/C	55.47%	60.66%	1	–
			G/C	40.89%	33.61%	1.88 (1.17–3)	0.009*
			G/G	3.64%	5.74%	0.76 (0.26–2.22)	0.62
		Dominant	C/C	55.47%	60.66%	1.69 (1.08–2.65)	0.023*
			G/C-/G/G	44.53%	39.34%		
		Recessive	C/C-G/C	96.36%	94.26%	0.6 (0.21–1.7)	0.334
			G/G	3.64%	5.74%		
		Additive	–	–	–	1.35 (0.92–1.96)	0.121
rs10036748	C/T	Co-dominant	T/T	55.47%	60.25%	1	–
			C/T	40.89%	34.02%	1.83 (1.14–2.92)	0.012*
			C/C	3.64%	5.74%	0.76 (0.26–2.2)	0.608
		Dominant	T/T	55.47%	60.66%	1.65 (1.05–2.59)	0.03*
			C/T-C/C	44.53%	39.34%		
		Recessive	T/T-C/T	96.36%	94.26%	0.6 (0.21–1.7)	0.334
			C/C	3.64%	5.74%		
		Additive	–	–	–	1.32 (0.91–1.93)	0.142

SNPs single nucleotide polymorphisms, *A* miner alleles, *B* major alleles, *HWE* Hardy–Weinberg equilibrium, *OR* odds ratio, *CI* confidence interval

P^a value was calculated by Wald' test with adjustment for gender, age, drinking and smoking status

$P=0.009$). And, based on the dominant model, rs7708392 was found correlating with a 1.69-fold higher risk of HCC in chronic HBV carriers ("G/C-G/G" vs. "C/C": OR 1.69, 95% CI 1.08–2.65, $P=0.023$). Additionally, we observed the genotype "C/T" of rs10036748 was more prevalent in case than controls compared with genotype "T/T" ("C/T" vs. "T/T": OR 1.83, 95% CI 1.14–2.92, $P=0.012$). Similarly, rs10036748 was associated with an increased risk of HBV-induced HCC based on dominant model ("C/T-C/C" vs. "T/T": OR 1.65, 95% CI 1.05–2.59, $P=0.03$). These results indicated that rs7708392 and rs10036748 polymorphisms played a dangerous role for the susceptibility of HBV-induced HCC. As for rs3792792, no difference genotype distribution was found between cases and controls.

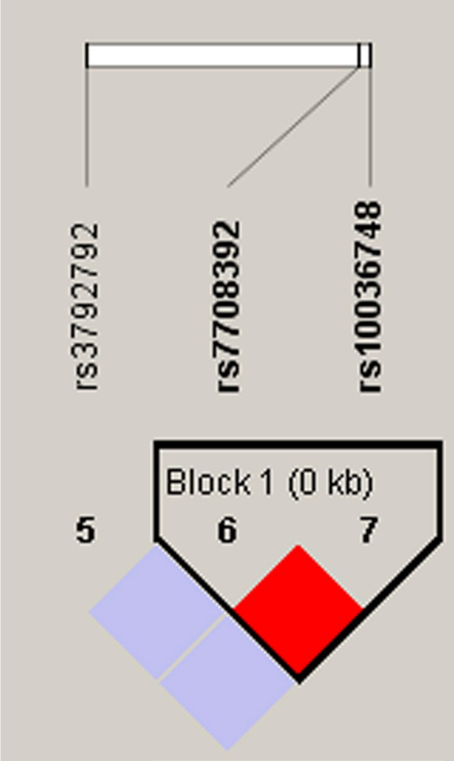

Fig. 1 LD analysis of candidate SNPs in TNIP1. LD plots containing 3 SNPs in TNIP1 genes, and standard color frame is used to show LD pattern. One block in the figure showed higher LD. D' value was 1

Finally, in the haplotype analysis, we used the allele frequency data from all the subjects to do an LD analysis. From the Fig. 1, rs7708302 and rs10036748 in *TNIP1* was detected to tend co-inherit, and the D' value was 1. Unfortunately, we didn't find a significant association between haplotypes and HBV-induced HCC risk in Table 5.

Table 5 The haplotypes of two SNPs (rs7708392 and rs10036748) in TNIP1 and the HBV-related HCC risk

Genes	SNPs	Haplotype	Haplotype frequency		P^a	With adjustment	
			Case	Control		95% CI	P^b
TNIP1	rs7708392lrs10036748	GC	0.2409	0.2254	0.5662	1.35 (0.92–1.96)	0.121
		CT	0.7591	0.7725	0.6192	0.76 (0.52–1.1)	0.141

SNPs single nucleotide polymorphisms, *OR* odds ratio. *CI* confidence interval

P^a value was calculated by Pearson's χ^2 test

P^b value was calculated by Wald' test with adjustment for gender, age, drinking and smoking status

Discussion

In this present study, we investigated the association between four selected TNIP1 SNPs and the risk of HBV-induced HCC in the Chinese Han population. We found that both rs7708392 and rs10036748 were associated with an increased risk of HBV-induced HCC. Our finds suggested that polymorphisms of TNIP1 may play an important role in the process of HBV-induced HCC.

TNIP1 gene is comprised of 18 exons, and encodes the protein TNIP1 which is wide distribution in tissue (Flores et al. 2011; Gurevich et al. 2011). TNIP1 has been regarded as an inhibitor of TNF-α receptor and toll receptor induced NF-κβ activation. Evidences have revealed that TNIP1 not only interacted with TNFα-induced protein 3 (A20) to inhibit the ubiquitination of NF-κβ essential modulator IKKγ (Mauro et al. 2006), but also decreased the activation of NF-κβ subunits p50 (Cohen et al. 2009), resulting in the NF-κβ signal transduction blocking. NF-κβ factor has been considered the central mediator in the inflammatory process and to be linked with the development of multiple malignancies (DiDonato et al. 2012; Li et al. 2015). Recent studies have reported that TNIP1 can interact with other proteins, especially down-signal pathway transduction factors, to inhibit its function, and plays a crucial role in inflammatory response and cell apoptosis (Khanolkar et al. 2016; Oshima et al. 2009). The interaction of protein–protein induced by TNIP1 involved in multiple receptor mediated signal pathway, containing membrane bound tumor necrosis factor-α receptor (Oshima et al. 2009), epidermal growth factor receptor (Zhang et al. 2002) and toll-like receptor (Nanda et al. 2011) signaling cascades, and nuclear peroxisome proliferator activated receptor (Gurevich et al. 2012) and retinoic acid receptor pathways (Gurevich and Aneskievich 2009). These pathways may likely contribute to the etiologies of diseases.

A growing number of publications have implicated *TNIP1* through genome-wide analysis studies in chronic inflammatory diseases, for example, systemic lupus erythematosus (SLE) (Alarcon-Riquelme et al. 2016; Han et al. 2009), psoriasis (Munir et al. 2015), and systemic sclerosis (Allanore et al. 2011). Furthermore, *TNIP1* polymorphisms were found related with the cancers risk. Minor allele "G" of rs7708392 and minor allele "C" of rs10036748 in *TNIP1* were correlated with an increased the risk of colorectal (Li et al. 2017) and gastric (Liu et al. 2016), but not esophageal (Yue et al. 2017) carcinomas. But, little information is found about the polymorphisms of rs3792792 and rs4958881 with cancer risk.

Depending on where the abnormal forms of SNPs presented, they may result in different effects, for example SNPs on coding region may induce the malformation of proteins structure and affect its function, and SNPs on regulatory or intron regions may lead to translation dysregulation. *TNIP1* rs7708392 and rs10036748 are located in intron which is a sequence that doesn't code protein but can regulate mRNA splicing. Thus, it is possible that the polymorphisms of these two SNPs may be associated with the selection of splicing variants, resulting in translating differ proteins. Our present study showed that polymorphisms of rs7708392 and rs10036748 polymorphisms in *TNIP1* gene were significantly related with the risk of HCC in chronic HBV carriers. Further analysis on the molecular mechanism involving these SNPs is required.

There are several limitations in this study. Firstly, our sample size is relatively small, so we hope to collect more samples in the future. Secondly, the subjects in present study were all Han Chinese who lived in Hainan province. The results found here need the support of other ethnic population data. Thirdly, the biological mechanism of genetic polymorphisms in *TNIP1* was not investigated in present study. It will be important to confirm our findings based on cell and molecular biology methods.

Conclusion

In summary, our results indicate a likelihood association between *TNIP1* and the risk of HBV-induced HCC, and *TNIP1* polymorphisms may be a harmful factor for the development of HCC in HBV carriers. Furthermore, the association of *TNIP1* polymorphisms with HBV-induced HCC susceptibility is indeed studied in bigger sample size and other ethnic populations.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there are no conflicts of interest.

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