

# Association of *TNIP1* polymorphisms with hepatocellular carcinoma in a Northwest Chinese Han population

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## Abstract

Study has demonstrated that *TNIP1* polymorphisms are associated with an increased risk of HBV-induced hepatocellular carcinoma (HCC). The purpose of this study was to investigate the correlation between polymorphisms in *TNIP1* and HCC risk in a Northwest Chinese Han population.

A case-control study was conducted including 473 Hepatocellular carcinoma patients and 564 healthy controls. Three SNPs (rs3792792, rs7708392, and rs10036748) were genotyped with Sequenom MassARRAY technology and their associations with HCC risk were analyzed. These data were evaluated using the Chi-square test/Fisher's exact test, genetic model analysis, and haplotype analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association.

Patients with the "G" allele of *TNIP1* rs7708392 showed a significantly increased risk of HCC (OR=1.24, 95%CI: 1.01–1.52,  $P=.042$ ). Significant association was also shown between *TNIP1* rs7708392 and HCC susceptibility in Additive model (OR=1.25; 95% CI=1.01–1.54;  $P=.040$ ). Besides, we also found that the "GC" haplotype of rs7708392 and rs10036748 was significantly associated with higher occurrence of HCC (OR=1.25, 95% CI: 1.01–1.54,  $P=.039$ ).

These results demonstrate that *TNIP1* polymorphisms are associated with increased HCC risk in a Northwest Chinese Han population for the first time, which warrants further investigation in the future.

**Abbreviations:** CIs = confidence intervals, CRC = colorectal cancer, HCC = hepatocellular carcinoma, LD = linkage disequilibrium, NF- $\kappa$ B = nuclear factor kappa- $\beta$ , ORs = odds ratios, SNP = single nucleotide polymorphisms, *TNIP1* = tumor necrosis factor- $\alpha$ -induced protein 3-interacting protein 1.

**Keywords:** genetic susceptibility, hepatocellular carcinoma, SNPs, *TNIP1*

## 1. Introduction

HCC is the second most common cause of mortality from any type of cancer in China, with an extremely high malignancy such

that the number of deaths (745,500) is similar to that of new cases (782,500) every year.<sup>[1–4]</sup> China and the Asia Pacific region are the highest incidence of HCC in the world.<sup>[5,6]</sup> The diagnosis of HCC is generally performed by imaging techniques, in combination with the dosage of plasmatic alpha-fetoprotein and histological analysis of tissue biopsies.<sup>[7,8]</sup> Therapeutic approaches for HCC include radical or palliative liver resection, radioactive seed implantation, transarterial chemoembolization, radiofrequency ablation, tumor immunotherapy, and liver transplantation.<sup>[9–11]</sup> But, HCC has poor prognosis with the overexpression of some risk genes, such as *PD-L1*, *PD-L2*, *Rabl3* and *Cullin7*.<sup>[12,13]</sup> Therefore, identifying genetic susceptibility and taking early prevention measures are necessary to prevent HCC.

Recent studies have shown the importance of single nucleotide polymorphisms (SNPs) in the development of HCC, such as *HLA-DP*, *hOSCP1*, *MDM2*.<sup>[14–16]</sup> Tumor necrosis factor- $\alpha$ -induced protein 3-interacting protein 1 (*TNIP1*), located on chromosome 5q32–33.1, encodes an A20-binding protein which plays an important role in autoimmunity, development, tissue homeostasis, chronic inflammation, and tumor progression through the inhibition of nuclear factor kappa-B (NF- $\kappa$ B) activation.<sup>[17]</sup> Cheng et al found *TNIP1* rs7708392 and rs10036748 were associated with an increased risk of HBV-induced HCC which including 248 HCC patients and 242 chronic HBV carriers.<sup>[18]</sup> However, whether *TNIP1* polymorphism is correlated with HCC risk for healthy population is still unknown.

Therefore, the objective of the present study was to evaluate the association of *TNIP1* polymorphism and HCC susceptibility

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YS and LZ contributed equally to this work.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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**Table 1**  
Primers used for the identification of *TNIP1* polymorphisms.

SNPs	First PCR (5'→3')	Second PCR (5'→3')	UEP SEQ (5'→3')
rs3792792	ACGTTGGATGCTCAGATCAGTTCACCTCTC	ACGTTGGATGATGGCAGCTGTTACGGCCAC	ccctTACGGCCACCACCAAGCATG
rs7708392	ACGTTGGATGAGGCCAACTGGTCAATTCTC	ACGTTGGATGGGGTCTCTCTGGAACCTAG	ggggaTGGAACTTAGTACTAGTCA
rs10036748	ACGTTGGATGGCAAAGCAGCCCTTTTTC	ACGTTGGATGCTTTCATAGCATGATACACG	ACGTATGAGAAAAATAAATAGTAA

PCR=PCR primer, SNPs=single-nucleotide polymorphisms; UEP=un-extended mini-sequencing primer.

between HCC patients and healthy controls in a Chinese Han population from Northwest China.

## 2. Materials and methods

### 2.1. Study subjects

All subjects were ethnically homogeneous Chinese Han and residents of Northwest China without restrictions of age, sex, or HCC stage. HCC patients were newly diagnosed through clinical and histopathologic examinations according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in the Inner Mongolia Autonomous Region People's Hospital from December of 2015 to December of 2019.<sup>[19]</sup> None of the HCC patients had history of other cancers. Controls were cancer, hepatitis or cirrhosis-free healthy populations who were randomly selected from the Physical Examination Center of this hospital in the same study period.

The study protocol was approved by the ethics committee of the Inner Mongolia Autonomous Region People's Hospital. Blood samples were collected from subjects with informed content.

### 2.2. DNA extraction

Genomic DNA was extracted from peripheral blood leukocytes in venous blood using the GoldMag-Mini Purification Kit (GoldMag Co Ltd, Xi'an city, China) according to the manufacturer's instructions, and quantified with a spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA) at wavelengths of A260 and A280 nm. DNA was diluted with QIAGEN to a final concentration of 20 ng/ $\mu$ L.

### 2.3. Selection of SNPs and method of genotyping

Using the HapMap database of the Chinese Han Beijing population, we searched SNPs from the *TNIP1* gene and restricted with a minor allele frequency (MAF) >5%. Three *TNIP1* SNPs associated with HBV-induced HCC risk in Southwest Chinese Han Population were chosen for analysis in this study. Primers for amplification process and single base extension reactions were designed with Sequenom Mass-ARRAY Assay Design 3.0 Software (Sequenom Co Ltd, San Diego, CA).<sup>[20]</sup> The corresponding primers used for each SNP in the present study are listed in Table 1. Sequenom Mass-ARRAY RS1000 (Sequenom, San Diego, CA) was applied to SNP genotyping. Data management and analysis were performed using Sequenom Typer 4.0 Software.<sup>[21]</sup>

### 2.4. Statistical analysis

Data were analyzed using SPSS version 18.0 statistical software (SPSS Inc, Chicago, IL) and Excel (Microsoft Corp, Redmond, WA). Age and gender were compared between HCC cases and

controls using Welch's *t* test and Pearson's  $\chi^2$  test, respectively. Allele frequency of each SNP in the control subjects was analyzed using  $\chi^2$  test to evaluate departure from Hardy-Weinberg equilibrium (HWE). Chi-square test/Fisher's exact test was used to compare the differences in SNP allele and genotype distribution between HCC cases and controls. The odds ratios (ORs) and 95% confidence intervals (CIs), used to assess the association between each SNP and the risk of HCC, were calculated using the logistic regression model with or without adjustment for age and gender. Genetic model analysis (Dominant, Recessive and Additive) were performed with PLINK software (<http://pngu.mgh.harvard.edu/purcell/plink/>) to assess the association of these SNPs. We used the Haploview software package (version 4.2) platform for analyses of pairwise linkage disequilibrium (LD) and haplotype structure.<sup>[22]</sup> The correlations between *TNIP1* haplotypes and HCC risk were also calculated by logistic regression analysis. Statistical significance was set at  $P < .05$  for all tests which were two-sided.

## 3. Results

### 3.1. Demographic characteristics

A total of 473 HCC cases and 564 healthy controls were enrolled in our study. There were significant differences in age ( $P < .05$ ) and gender ( $P < .05$ ) between the two groups (Table 2). Therefore, the variable of age and gender was adjusted further for eliminating any residual confounding effect in multivariate logistic regression analysis.

### 3.2. Associations between *TNIP1* polymorphisms and the risk of HCC

The candidate *TNIP1* SNPs (rs3792792, rs7708392, and rs10036748) were genotyped in HCC patients and healthy controls. Table 3 shows the minor allele distributions of *TNIP1* SNPs and their relationships with HCC susceptibility. The three SNPs were all in line with Hardy-Weinberg equilibrium in controls ( $P > .05$ ). We compared the differences in frequency distributions of alleles between HCC cases and controls and found one significant SNP (rs7708392) was associated with HCC

**Table 2**  
Distributions of gender and age in HCC cases and controls.

Variables	Cases (n = 473)	Controls (n = 564)	P
Sex (%)			<.05 <sup>a</sup>
Male	390 (82.5)	339 (60.1)	
Female	83 (17.5)	225 (39.9)	
Age, year	55.83	53.92	<.05 <sup>b</sup>

P values were calculated from Welch's *t* test and Pearson's  $\chi^2$  test.

**Table 3**  
Basic information on candidate *TNIP1* polymorphisms and their associations with HCC.

SNPs	Allele	Minor allele frequency		HWE <i>P</i> value	OR	95%CI	<i>P</i> <sup>a</sup>	Gene
		Case	Control					
rs3792792	C/T	0.063	0.051	1.000	1.25	0.86–1.81	.240	<i>TNIP1</i>
rs7708392	G/C	0.247	0.209	.444	1.24	1.01–1.52	.042*	<i>TNIP1</i>
rs10036748	C/T	0.247	0.211	.527	1.23	1.00–1.51	.053	<i>TNIP1</i>

95%CI=95% confidence interval, HWE=Hardy–Weinberg equilibrium, OR=odds ratio, SNPs=single-nucleotide polymorphisms.

<sup>a</sup> *P* values were calculated from Pearson Chi-Square test.

\* *P* < .05 indicates statistical significance.

**Table 4**  
Association between *TNIP1* rs7708392 and HCC susceptibility under multiple inheritance models.

SNP	Models	Genotype	Case (%)	Control (%)	Without adjustment			With adjustment		
					OR	95% CI	<i>P</i>	OR	95% CI	<i>P</i>
rs7708392 (C > G)	Genotype	CC	266 (56.36%)	349 (61.88%)	1			1		
		GC	179 (37.92%)	194 (34.40%)	1.21	0.94–1.57	.147	1.19	0.91–1.55	.209
		GG	27 (5.72%)	21 (3.72%)	1.69	0.93–3.05	.084	1.45	0.79–2.68	.231
	Dominant	CC	266 (56.36%)	349 (61.88%)	1			1		
		GC+GG	206 (43.64%)	215 (38.12%)	1.26	0.98–1.61	.072	1.21	0.94–1.57	.140
	Recessive	CC+GC	445 (94.28%)	543 (96.28%)	1			1		
		GG	27 (5.72%)	21 (3.72%)	1.57	0.88–2.81	.131	1.36	0.74–2.49	.317
	Additive	–	–	–	1.25	1.01–1.54	.040*	1.20	0.96–1.48	.108

*P* values were calculated by unconditional logistic regression analysis with or without adjustments for age and gender.

\* *P* < .05 indicates statistical significance.

risk. Significant difference was observed in allele frequency of rs7708392G between cases and controls (24.7% vs 20.9%). And the “G” allele of rs7708392 showed significantly increased risk of HCC (OR = 1.24, 95%CI: 1.01–1.52, *P* = .042).

Next, after evaluating the potential association under dominant, recessive, and additive genetic models, we found one SNP was associated with increased risk of HCC without the adjustment: rs7708392 under an additive model (OR = 1.25, 95%CI: 1.01–1.54, *P* = .040) (Table 4). For the rest of SNPs (rs3792792 and rs10036748), neither their allele distributions nor genetic model analysis was found to be significantly associated with the risk of HCC.

### 3.3. Haplotype analysis

In Figure 1, the red squares of the *TNIP1* linkage disequilibrium block exhibited statistically significant linkage between rs7708392 and rs10036748. Finally, we listed the haplotypes with frequencies of >0.05 and their associations with HCC risk in Table 5. Frequency <0.05 will be ignored in analysis. We found that the “GC” haplotype of rs7708392 and rs10036748 was associated with increased risk of HCC before the adjustment (OR = 1.25; 95% CI, 1.01–1.54; *P* = .039). But after adjustment, the GC haplotype was found to be irrelevant to HCC (OR = 1.20; 95% CI, 0.96–1.48; *P* = .11). The CT haplotype was also found to be irrelevant to HCC.

### 4. Discussion

In this study, we found that the “G” allele of *TNIP1* rs7708392 was associated with increased risk of HCC. We also observed that the “GC” haplotype of rs7708392 and rs10036748 in *TNIP1* was associated with a 25% increase in the risk of HCC. These results suggest that *TNIP1* polymorphisms are significantly associated with higher occurrence of HCC in a Northwest Chinese Han population.

*TNIP1* encodes an A20-binding protein which can regulate the activation of nuclear factor kappa-β (NF-κβ).<sup>[17]</sup> Increased NF-κβ activity has been suggested to be involved in the malignant behavior of EGFR-overexpressing cells.<sup>[23–25]</sup> Huang et al showed the A20-binding protein inhibits EGFR-mediated NF-κβ activation and growth of EGF receptor-overexpressing tumour cells.<sup>[26]</sup> Therefore, we regarded *TNIP1* as a “protective” gene that may be involved in the inhibition of HCC development. However, in the present study, we found *TNIP1* polymorphisms are significantly associated with increased risk of HCC, which may be due to down-regulate expression of *TNIP1* gene by polymorphisms.

A previous study indicated that minor allele “G” of rs7708392 in *TNIP1* was significantly associated with an increased

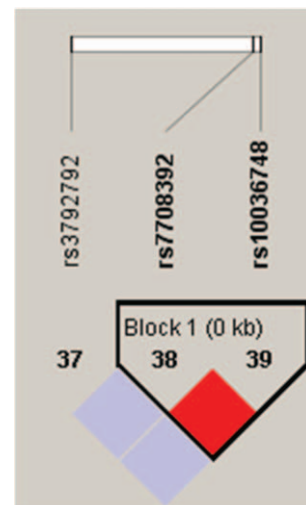


Figure 1. Haplotype block map for part of the SNPs in the *TNIP1* gene.

**Table 5**  
**TNIP1 haplotype frequencies and their associations with HCC risk.**

Haplotype block	Haplotype frequencies		Without adjustment		With adjustment	
	Case	Control	OR (95%CI)	P	OR (95%CI)	P
GC	0.25	0.21	1.25 (1.01–1.54)	.039*	1.20 (0.96–1.48)	.11
CT	0.75	0.79	0.81 (0.66–1.00)	.051	0.84 (0.68–1.05)	.12

95%CI=95% confidence interval, OR=odds ratio.

P values were calculated from unconditional logistic regression analysis.

\* P<sub>≤</sub>.05 indicates statistical significance.

colorectal cancer (CRC) risk. And they also observed that the haplotype “GC” of rs7708392 and rs10036748 was more frequent among CRC patients and correlated with a 1.58-fold increased CRC susceptibility in Chinese Han population.<sup>[27]</sup> In this study, we similarly found the two *TNIP1* SNPs rs7708392 and rs10036748 were in strong linkage disequilibrium in our subjects and “GC” haplotype of rs7708392 and rs10036748 was significantly associated with increased risk of HCC. Taken together, these data provide support for the notion that *TNIP1* polymorphisms might have similar effects on carcinoma risk in same population of China.

Cheng et al reported that both *TNIP1* rs770839 “G” and rs10036748 “C” were correlated with an increased risk of HBV-induced HCC. In haplotype analysis, no significant association between haplotypes and the HCC risk in HBV carriers was found.<sup>[18]</sup> In the present study, controls were hepatitis-free healthy populations who were different from the controls of chronic HBV carriers in Cheng et al. However, similar results were obtained on *TNIP1* polymorphism with increased risk of HCC, which suggest that *TNIP1* polymorphism is a risk factor of HCC for either chronic HBV carriers or hepatitis-free healthy populations of China.

There are some limitations to the present case–control study. First, the sample size of our study was relatively small, which may mean that the study was underpowered. Second, the ethnicity of study participants was limited to the Han Chinese population. Whether the conclusions of the present study can also be drawn in other human races still need to be clarified. Third, many other risk factors (e.g., smoking, alcohol drinking) were not included due to a lack of corresponding clinical information. Finally, the function genetic variants and mechanisms underpinning this association will require additional studies. We believe that our results will encourage further studies using large sample sizes and help elucidate the underlying mechanisms of *TNIP1* polymorphisms conferring susceptibility to HCC.

In conclusion, the present study provides evidence that *TNIP1* polymorphisms contribute to the susceptibility of HCC in a Northwest Chinese Han population, which may provide new data for screening of HCC susceptibility in Chinese Han population and shed new ideas for researchers to further study the mechanism of HCC.

### Author contributions

**Data curation:** Yuting Shi, Lihua Zhang.

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**Supervision:** Pengfei Wu, Xiaoli Zhang.

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**Writing – review & editing:** Yuting Shi, Xiaoli Zhang.

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