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The ERCC1-4533/8092, TNF-α 238/308 polymorphisms and the risk of hepatocellular carcinoma in Guangxi Zhuang populations of China

Case-control study

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Abstract

Objective: To investigate the relationship between excision repair cross-complementing group 1 (ERCC1)-4533/8092, tumor necrosis factor-alpha (TNF-α)-238/308 polymorphisms, and the risk of hepatocellular carcinoma (HCC) in Guangxi Zhuang population of China.

Methods: Polymerase chain reaction-restriction fragment length polymorphism method was used to detect the ERCC1-4533/8092 and TNF-α-238/308 polymorphisms in 88 cases with HCC and 82 cases of normal control.

Results: There were no differences in the frequency distribution of ERCC1-4533 and TNF-α-238 polymorphisms in the HCC group and the control group ($P > 0.05$). The genotype frequency distributions of the ERCC1-8092 and TNF-α-308 in the HCC group and the control group were different ($P < 0.05$). Compared with ERCC1-8092 CC genotype, ERCC1-C8092 CA/AA genotype had higher risk of HCC (CA/AA vs CC; odds ratio 3.51, 95% confidence interval 1.03–12.016). Compared with TNF-α-308 GG genotype, TNF-α-308 GA/AA genotype was significantly associated with an increased risk of HCC (GA/AA vs GG; odds ratio 3.84, 95% confidence interval 1.011–14.57).

Conclusion: The genetic polymorphisms of ERCC1-8092 and TNF-α-308 are associated with the risk of HCC in Guangxi Zhuang population of China.

Abbreviations: 95% CIs = 95% confidence intervals, ERCC1 = excision repair cross-complementing group 1, HCC = hepatocellular carcinoma, MHC = major histocompatibility complex, ORs = odds ratios, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, TNF-α = tumor necrosis factor-alpha.

Keywords: ERCC1, hepatocellular carcinoma, polymorphisms, TNF-α, Zhuang

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide, ranking third in global cancer-related deaths.[1] At present, the number of patients with HCC in China accounts for about 50% of the total number of cases and deaths globally.[2]

Guangxi is not only the region of the Zhuang population, but also has one of the high incidences of HCC in China. Most of the patients are diagnosed with HCC when they are in the advanced stage of the disease, a majority of parents with HCC have a poor prognosis, and the 5-year survival rate is low. Therefore, the early diagnosis of HCC is becoming more and more important. Previous studies showed that different genetic polymorphisms may be related to the risk of different cancers.[3] But the effect of single-nucleotide polymorphisms on susceptibility to cancer is controversial.

Excision repair cross-complementing group 1 (ERCC1) is one of the key enzyme that plays an important role in nucleotide excision repair pathway, and ERCC1 gene polymorphisms may influence nucleotide excision repair process, increase the susceptibility to cancers, including colorectal cancer, glioma, nonsmall cell carcinoma, and gastric cancer.[4–7] Tumor necrosis factor-alpha (TNF-α) encodes a proinflammatory cytokine that is secreted primarily by macrophages, monocytes, neutrophils, T cells, and natural killer (NK) cells, and plays critical roles in the pathogenesis of inflammatory autoimmune and malignant diseases.[8,9] Several studies have indicated that several polymorphisms in the promoter region of TNF-α are associated with the risk of some types of cancers, such as urogenital cancer, non-Hodgkin lymphomas, gastric cancer, and breast cancer.[10–13]

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However, few studies have explored the ERCC1 and TNF-α polymorphisms and risk of hepatocellular carcinoma. Therefore, in this case-control study, we would investigate the relationship between polymorphisms of ERCC1, TNF-α, and the risk of HCC in Guangxi Zhuang populations of China, which would be useful to the disease diagnosis and personalized treatment and prognosis.

2. Materials and methods

2.1. Patients

In this case-control study, a total of 170 Chinese Zhuang subjects were selected, and the HCC group included 88 hepatocellular carcinoma cases, who were diagnosed by imaging examination and pathological examination from July 2015 to December 2015 in the Affiliated Tumor Hospital of Guangxi Medical University, and HCC cases were collected from new admitted patients, who were the first diagnosis of hepatocellular carcinoma, and the blood samples were collected before treatment (including surgical resection, radiotherapy, chemotherapy, etc.).Also, the control group included cancer-free subjects; 82 cases (clinical and laboratory examination were normal, no family history of tumor) were selected from the same hospital in the same period. There were 72 males and 16 females in the HCC group, and 67 males and 15 females in the control group. The mean age of HCC group was 51.375 years, and the mean age of control group was 53.341 years. There were no significant differences in the age and sex distribution between the HCC group and the control group ($P > 0.05$). For other characteristics, smoking status was not significantly different between the HCC group and the control group ($P > 0.05$). Alcohol consumption, hepatitis B surface antigen, and serum alpha fetoprotein levels were significantly different in the HCC group and control group ($P < 0.05$). Table 1 showed all the characteristics of studied subjects. All patients signed the informed consents, and reported by the Medical Ethics Committee of Guangxi Medical University approval.

2.2. DNA extraction

All subjects were asked to provide 3 to 5 mL peripheral blood in ethylene diamine tetraacetic Aci anticoagulant tubes. Genomic DNA was extracted from the samples using the Rapid Extraction of Whole Blood Genomic DNA Kit (Aidlab; Beijing, China) following the manufacturer's instructions. DNA concentration was determined by the NanoDrop 1000 Spectrophotometer (Thermo Scientific, Wilmington, DE), which was stored at −20°C until use.

2.3. Polymorphism genotyping

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to analyze the polymorphisms of the ERCC1-4533/8092 and TNF-α-238/308. The total volume of PCR reaction system was 25 μL, which contained 5 u/μL Taq DNA, polymerase 0.5 μL, genomic DNA template 1 μL,10 μmol/L upstream, and downstream primers 1 μL, 2.5 mmol/L dNTPs 2 μL,10× PCR buffer (Mg2+Plus) 2.5 μL, sterile water 17 μL. Amplification was performed in ProFlex PCR thermocycler (Life Technologies). PCR products were then digested overnight by Restriction enzymes (TaKaRa, Japan) at 37°C. The PCR products and enzyme digestion products were run on 2% agarose gel electrophoresis and visualized by ethidium bromide staining under ultraviolet light. For quality control, 10% of subjects were randomly selected to repeat analysis. The results were in 100% agreement with the first time. PCR reaction conditions and related information of PCR-RFLP were shown in Table 2.

2.4. Statistical analysis

All analyses were conducted using the SPSS 17.0 statistical software (SPSS Inc., Chicago, IL). Continuous variables were expressed as the means ± SD, whereas categorical variables were reported as frequencies and percentages (%). Comparison between the HCC group and the control group were used by the Student *t* test. Hardy–Weinberg equilibrium of the genotype

Table 1

Clinical characteristics of the HCC and controls groups.

Characteristics	Groups				χ^2	*P*
	HCC (n)		Control (n)			
	n	%	n	%		
Age, y						
<50	37	42.05	35	42.68	0.01	0.93
≥50	51	57.95	47	57.32		
Sex						
Male	72	81.82	67	76.14	3.50×10^{-4}	0.98
Female	16	18.18	15	24.86		
Alcohol consumption						
Yes	29	32.95	13	15.85	6.67	0.01
No	59	67.05	69	84.15		
Smoking status						
Yes	32	32.65	16	19.51	3.94	0.47
No	66	67.35	66	80.49		
HBsAg						
+	80	90.91	10	11.36	105.57	<0.01
−	8	9.09	72	88.64		
Serum AFP levels						
<400 ng/mL	45	48.86	81	1.14	50.23	<0.01
≥400 ng/mL	43	51.14	1	99.86		

AFP = alpha fetoprotein, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma.

Table 2

PCR reaction conditions and related information of PCR-RFLP.

Genotype	Primer sequences	PCR condition	PCR products length	Restriction enzyme	Size for PCR-RFLP
ERCC1-4533	F: 5′-AGATGTCCTCTGCTCACCCC-3′	94°C 5 min;35 cycles for 94°C 1 min, 61°C 45 s,72°C 1 min;72°C 10 min	379 bp	*PmaC*I	AA: 379 bp
	R: 5′-GGGAGAACAAAGTGGCTGGA-3′				GA: 174 bp, 205 bp, 379 bp
					GG: 174 bp, 205 bp
ERCC1-8092	F: 5′-ACAGTGCCCCAAGAGGAGAT-3′	95°C 5 min;35 cycles for 95°C 45 s, 59°C 30 s, 72°C 45 s;72°C 10 min	204 bp	*Mbo*II	AA: 116 bp, 88 bp
	R: 5′-AGTCTCTGGGGAGGGATTCT-3′				CA: 204 bp, 116 bp, 88 bp
					CC: 204 bp
TNF-α-238	F: 5′-AGAAGACCCCCCTCGGAACC-3′	95°C 5 min;35 cycles for 94°C 45 s,60°C 30 s, 72°C 45 s;72°C 10 min	152bp	*Msp*I	GG: 133 bp, 19 bp
	R: 5′-ATCTGGAGGAAGCGGTAGTG-3′				GA: 152 bp, 133 bp, 19 bp
					AA: 152bp
TNF-α-308	F: 5′-AGGCAATAGGTTTTGAGGGCCAT-3′	94°C 5 min;35 cycles for 94°C 45 s,61°C 30 s, 72°C 45 s, 72°C 10 min	117 bp	*Nco*I	GG: 87 bp, 20 bp
	R: 5′-TCCTCCCTGCTCCGATTCCG-3′				GA: 107 bp, 87 bp, 20 bp
					AA: 107 bp

ERCC1 = excision repair cross-complementing group 1, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, TNF-α = tumor necrosis factor-alpha,

distribution in the control group and the distribution of allele and genotype frequencies in HCC group and control group were tested by chi-square test or Fisher exact test. Conditional logistic regression analysis was performed to evaluate the association between ERCC1 and TNF-α polymorphisms, and the risk of HCC. The association between the susceptibility to HCC and gene polymorphisms was analyzed using odds ratios (ORs) and 95% confidence intervals (95% CIs). All analyses were 2-sided; when $P < 0.05$, the difference was considered to be statistically significant.

3. Results

3.1. Genotype frequencies

The genotype distribution of ERCC1-4533/8092 and TNF-α-238/308 in the control group was consistent with the Hardy–Weinberg equilibrium ($P < 0.05$). The results of Hardy–Weinberg equilibrium were shown in Table 3.

Genotype distribution and allele frequencies of ERCC1-4533/8092 and TNF-α-238/308 in HCC group and control group are shown in Table 4. The results of PCR amplification products and agarose electrophoresis results of ERCC1-4533/8092 are shown in Figs. 1–4. For ERCC1, there were no statistical differences in the genotype distribution and allele frequencies of ERCC1-4533 genotype between the HCC group and the control group ($P > 0.05$). The genotype distribution and allele frequencies of ERCC1-8092 showed significant difference between the HCC group and the control group ($P < 0.05$). For TNF-α, the TNF-α-238 AA genotype was not found in this case-control study. The differences in the genotype distribution and allele frequencies of TNF-α-238 between the HCC group and the control group had no statistical significance ($P > 0.05$). The genotype distribution and allele frequencies of TNF-α-308 in the HCC group were significant with those of the control group ($P < 0.05$).

3.2. Association between polymorphisms and clinical characteristics and the risk of hepatocellular carcinoma

As shown in Table 5, The results of conditional logistic regression analysis showed that the carriers of ERCC1-8092 CA/AA genotype and A allele had significantly increased risk of HCC,

Table 3

Hardy–Weinberg equilibrium test for genotype distribution.

Genotype		Controls					
		Observed		Expected			
		n	%	n	%	χ^2	P
ERCC1-4533	GG	48	58.54	51.52	62.83		
	GA	34	41.46	30.37	37.04	0.41	0.82
	AA	0	0.00	0.10	0.13		
ERCC1-8092	CC	55	67.07	56.39	68.77		
	CA	26	31.71	23.22	28.32	0.61	0.80
	AA	1	1.22	2.39	2.91		
TNF-α-238	GG	66	80.49	66.78	81.44		
	GA	16	19.51	14.44	17.61	1.09	0.84
	AA	0	0.00	0.78	0.95		
TNF-α-238	GG	71	86.59	71.37	87.04		
	GA	11	13.41	10.26	12.52	0.04	0.98
	AA	0	0.00	0.37	0.44		

ERCC1 = excision repair cross-complementing group 1, TNF-α = tumor necrosis factor-alpha,

Table 4

Genotype distributions and allele frequencies of ERCC1-4533/8092 and TNF-α-238/308 in HCC group and control group [n (%)].

Genotype/allele		HCC group		Control group		χ^2	*P*
		n	%	n	%		
ERCC1-4533	GG	50	56.82	48	58.54		
	GA	37	42.05	34	41.46	0.90	0.99
	AA	1	1.13	0	0.00		
ERCC1-4533	G	137	77.84	130	79.27	0.10	0.75
	A	39	22.16	34	20.73		
ERCC1-8092	CC	36	40.90	55	67.07		
	CA	46	52.27	26	31.71	12.72	0.001
	AA	6	6.83	1	1.22		
ERCC1-8092	C	118	67.05	136	82.93	11.33	0.001
	A	58	32.95	28	17.07		
TNF-α-238	GG	70	79.55	66	80.49		
	GA	18	20.45	16	19.51	0.02	0.88
	AA	0	0.00	0	0.00		
TNF-α-238	G	158	89.77	148	90.24	0.02	0.88
	A	18	10.23	16	9.76		
TNF-α-308	GG	57	64.77	71	86.59		
	GA	30	34.09	11	13.41	11.18	0.002
	AA	1	1.14	0	0.00		
TNF-α-308	G	144	81.82	153	93.29	10.12	0.001
	A	32	18.18	11	6.71		

ERCC1 = excision repair cross-complementing group 1, HCC = hepatocellular carcinoma, TNF-α = tumor necrosis factor-alpha,

which ERCC1-8092 CC genotype and C allele were used as the reference (CA/AA vs CC; OR 3.51, 95% CI 1.03–12.016). For TNF-α-308, subjects with the TNF-α-308 GA/AA genotype and A allele were significantly associated with an increased risk of HCC as compared with GG genotype and G allele (GA/AA vs GG; OR 3.84, 95% CI 1.011–14.57). However, we found that the ERCC1-4533 and TNF-α-238 polymorphisms were not associated with the susceptibility of HCC.

4. Discussion

Over the past years, many case-control studies have been reported about the relationship between polymorphisms and susceptibility to HCC. But the study on the effect of population distribution on the susceptibility to HCC is less. For ERCC1, the number of articles on the ERCC1 gene polymorphisms and susceptibility to HCC is rare. For TNF-α, we only found few articles about the effect of population distribution on TNF-α polymorphisms and susceptibility to HCC. For example, the study by Feng et al[14] was based on the Han population, and the results were consistent with our study. In the study by Hu et al[15], the research objects were classified by country, and not by ethnicity.

The ERCC1 gene is located on the human chromosome 19q13.2-13.3. ERCC1 polymorphisms may influence the expression of ERCC1 mRNA, and ERCC1 protein function may affect the ability of nucleotide excision repair pathway, increase genomic instability, lead to increased genomic instability, and cause the occurrence of various cancers or other malignant diseases. Some studies have indicated that ERCC1 polymorphisms are closely related to the pathogenesis of various tumors, the response to platinum-based chemotherapy, and influence the prognosis of diseases, such as nonsmall cell lung cancer, gastric cancer, and ovarian cancer.[16–18] In this case-control study, our results suggested that the polymorphisms of ERCC1-8092 were associated with the incidence of HCC. While,

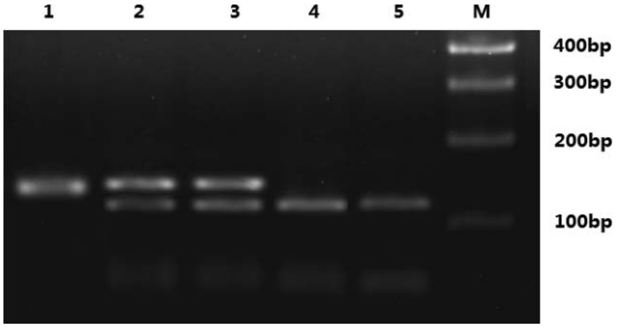

Figure 1. Results of 2% agarose gel electrophoresis of TNF-α-238 PCR products and *Msp*I enzyme digestion products. 1: TNF-α-238 PCR products; 2, 3: G/A heterozygote (152, 133, 19 bp); 4, 5: G/G homozygote (133, 19 bp); M: 100 bp DNA marker ladder. PCR = polymerase chain reaction, TNF-α = tumor necrosis factor-alpha,

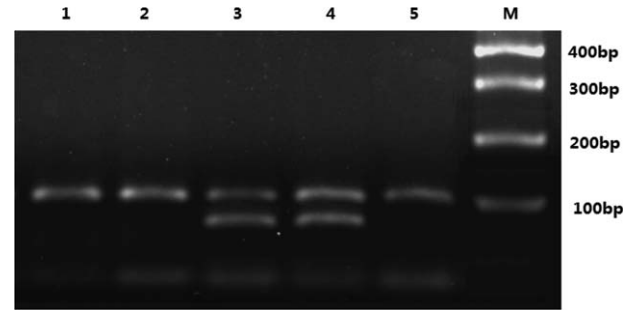

Figure 2. Results of 2% agarose gel electrophoresis of TNF-α-308 PCR products and *Nco*I enzyme digestion products. 1: A/A homozygote (107 bp); 2: G/A heterozygote (107, 87, 20 bp); 3, 4: G/G homozygote (133, 19 bp); 5: TNF-α-308 PCR products; M: 100 bp DNA marker ladder. PCR = polymerase chain reaction, TNF-α = tumor necrosis factor-alpha,

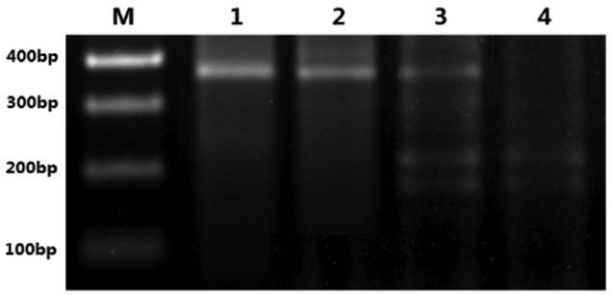

Figure 3. Results of 2% agarose gel electrophoresis of ERCC1-4533 PCR products and *Pma*CI enzyme digestion products. M: 100 bp DNA marker ladder; 1: ERCC1-4533 products; 2: A/A homozygote (379 bp); 3: G/A heterozygote (174, 205, 379 bp); 4: G/G homozygote (174, 205 bp). ERCC1 = excision repair cross-complementing group 1.

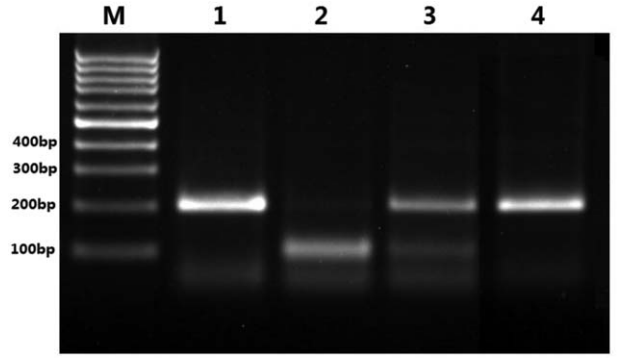

Figure 4. Results of 2% agarose gel electrophoresis of ERCC1-8092 PCR products and *Mbo*II enzyme digestion products. M: 100 bp DNA marker ladder; 1: ERCC1-8092 PCR products; 2: A/A homozygote (116, 88 bp); 3: C/A heterozygote (204, 116, 88 bp); 4: C/C homozygote (204 bp). ERCC1 = excision repair cross-complementing group 1, PCR = polymerase chain reaction.

the genotype distribution and allele frequencies of ERCC1-4533 were similar in the HCC group and the control group. Conditional logistic regression analysis demonstrated that CA/AA genotype of ERCC1-8092 might be a risk factor for HCC; the risk of carrying CA/AA genotype of ERCC1-8092 was 3.51 times that of C allele of ERCC1-8092.

The TNF-α gene is located within the major histocompatibility complex (MHC) region on chromosome 6p21. Some previous studies found that TNF-α-308 A allele can influence the expression of TNF-α. When G allele is replaced by A allele, the gene mutation leads to an increased constitutive and inducible expression levels of TNF-α. TNF-α-308 A SNP is linked with inflammation, autoimmune diseases, infectious diseases, and malignant diseases,[19–21] and the function of the TNF-α-238 polymorphism is not yet clear, and the results are still controversial. Huang et al[22] found that the risk of HCC in patients with TNF-α-238 GA genotype were 2.786 times higher than that of TNF-α-238 GG genotype carriers. Tian et al[23] revealed that TNF-α-238 polymorphisms were significantly associated with increased risk of liver cancer. Yang et al[24] indicated that the polymorphisms on TNF-α-308 sites did not increase the risk of HCC. Feng et al[14] showed that TNF-α-308 polymorphisms were associated with increased HCC risk in a Han Chinese population. In this study, our results showed that the genotype distribution and allele frequencies of TNF-α-238 polymorphisms did not differ between the HCC group and the control group, whereas TNF-α-308 polymorphisms were considered to be associated with the susceptibility of HCC, the risk of hepatocellular carcinoma in subjects with TNF-α-308 GA/AA genotypes was 3.84-fold than that of GG genotype, respectively.

The different results between our study and previous studies may be due to the sample size, the research method, the difference of the gene distribution in different geographical populations, and by chance. Because the number of subjects in this study was small and the populations were only in Guangxi Zhuang region. It is necessary to determine whether the polymorphisms of ERCC1-4533/8092 and TNF-α-238/308 will affect the susceptibility of HCC in larger sample size and different ethnic groups.

5. Conclusions

In conclusion, our study revealed that the polymorphisms of TNF-α and ERCC1 showed a differential distribution from patients in Guangxi Zhuang Autonomous Region with HCC. ERCC1-8092 and TNF-α-308 polymorphisms were associated with susceptibility to HCC, but it has not been found that the polymorphisms of ERCC1-4533 and TNF-α-238 were related to the occurrence and development of HCC. The results of this study may have great significance in the pathogenesis, individualized diagnosis, treatment and prognosis of HCC, and some references of the study of the relation between disease susceptibility and genetic polymorphisms in different ethnic group in the future.

Table 5

Conditional logistic regression analysis for the risk of hepatocellular carcinoma.

Factors		HCC [n (%)]	Control [n (%)]	OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
ERCC1-4533	GG	50 (56.82%)	48 (58.54%)	1.00		1.00	
	GA/AA	37 (44.31%)	34 (41.46%)	1.02 (0.56-1.89)	0.938	1.236 (0.38-4.00)	0.72
ERCC1-8092	CC	36 (40.91%)	55 (67.07%)	1.00		1.00	
	CA/AA	52 (59.09%)	27 (32.93%)	2.94 (1.57-5.51)	<0.001	3.51 (1.03-12.016)	0.04
TNF-α-238	GG	70 (79.54%)	66 (80.49%)	1.00		1.00	
	GA/AA	18 (20.46%)	16 (19.51%)	1.06 (0.50-2.25)	0.88	1.97 (0.50–7.80)	0.339
TNF-α-308	GG	57 (64.77%)	71 (86.59%)				
	GA/AA	30 (34.09%)	11 (13.41%)	3.34 (1.54–7.23)	0.002	3.84 (1.011–14.57)	0.04

CI = confidence interval, ERCC1 = excision repair cross-complementing group 1, HCC = hepatocellular carcinoma, OR = odds ratio, TNF-α = tumor necrosis factor-alpha,
* Adjusted for age, sex, smoking, drinking, HBsAg, and AFP.

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