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ORIGINAL RESEARCH

Investigation of *LEP* and *LEPR* polymorphisms with the risk of hepatocellular carcinoma: a case–control study in Eastern Chinese Han population

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Background: Leptin (*LEP*) and LEP receptor (*LEPR*) polymorphisms may be associated with the development of cancer.

Methods: In this study, we selected five functional *LEP* and *LEPR* single-nucleotide polymorphisms (SNPs) and conducted a case–control study to determine the relationship of *LEP* and *LEPR* polymorphisms with hepatocellular carcinoma (HCC) risk in Eastern Chinese Han population. There were 584 HCC cases and 923 cancer-free controls included in our study. HCC patients and controls were fully matched by age and sex. SNPscan™ genotyping method was used to analyze the genotyping of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A SNPs.

Results: We found that *LEP* rs7799039 A>G and rs2167270 G>A polymorphisms were associated with the susceptibility of HCC in this population (*LEP* rs7799039 A>G: GG vs AA: adjusted odds ratio [OR]=2.03, 95% CI, 1.22–3.38, *P*=0.006 and GG vs AA/AG: adjusted OR=1.97, 95% CI, 1.20–3.22, *P*=0.007; rs2167270 G>A: AA vs GG: adjusted OR=2.03, 95% CI, 1.10–3.75, *P*=0.024 and AA vs GG/GA: adjusted OR=2.01, 95% CI, 1.10–3.68, *P*=0.023). However, *LEPR* rs6588147 G>A polymorphism decreased the risk of HCC (GA vs GG: adjusted OR=0.62, 95% CI, 0.45–0.86, *P*=0.005 and AA/GA vs GG: adjusted OR=0.64, 95% CI, 0.47–0.88, *P*=0.007).

Conclusion: This case–control study highlights that *LEP* rs7799039 A>G and rs2167270 G>A polymorphisms increase the susceptibility to HCC; however, *LEPR* rs6588147 G>A polymorphism may be a protective factor for HCC in Eastern Chinese Han population.

Keywords: LEP, LEPR, polymorphism, hepatocellular carcinoma, risk, single nucleotide polymorphism, hepatitis B virus

Introduction

Liver cancer (LC) rates are the lowest in the South-Central areas of Asia and Northern, Central, and Eastern regions of Europe and the highest in East and South-East Asia and Northern and Western Africa.[1] China alone accounts for about 50% of the total number of LC patients and LC-related deaths.[1,2] Also, most of the LC patients have hepatocellular carcinoma (HCC). Although chronic hepatitis B virus (HBV) infection contributes to the major etiology of HCC,[3] other risk factors may also influence the development of HCC. Nowadays, obesity and overweight are becoming a prevalent problem, which may increase the susceptibility to various cancers.[4] Fatty liver is found commonly in patients with chronic HBV infection and might potentiate the risk of HBV-associated HCC by 7.3-fold.[5] It is thought that metabolism-related gene may influence the risk of HCC.

The excess of macronutrients stored results in overweight and obesity. Adipocytes may release many inflammatory mediators and lead to oxidative stress and

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proinflammatory states.[6] Inflammatory and oxidative stress are related to the development of malignancy.[7,8] Leptin (LEP) and LEP receptor (LEPR) may be implicated in various signal pathways, such as JAK/STAT, MAPK, PI3K, and mTOR.[9] Also, these signal pathways were suggested to be correlated with carcinogenesis.[10,11] Soga et al reported that fatty liver Shionogi-Lep/Lep mice developed hepatocellular adenomas and carcinomas following steatohepatitis.[12] In addition, high levels of LEP were found in sera of patients with HCC.[13] Thus, *LEP* and *LEPR* genes may impact on signal pathways and play an important role in the development of HCC.

Recently, some important *LEP* and *LEPR* single-nucleotide polymorphisms (SNPs) were explored for the susceptibility to a number of cancers. *LEP* rs7799039 A>G, a promoter SNP, was suggested this variant was particularly affecting transcriptional level and LEP expression.[14] However, *LEP* rs2167270 G>A is located in 5′-untranslated region and correlated with the translation process of *LEP* mRNA. Some previous meta-analyses suggested that *LEP* rs7799039 A>G and rs2167270 G>A variants conferred risk to cancer.[15–17] However, the association of *LEP* rs7799039 A>G and rs2167270 G>A polymorphisms with HCC risk is unknown.

LEPR rs1137100 G>A and rs1137101 G>A polymorphisms are two missense SNPs. Li et al reported that rs1137100 G>A and rs1137101 G>A polymorphisms in *LEPR* gene were correlated with susceptibility to HCC.[18] In individuals with chronic HBV infection, these two *LEPR* SNPs may be a biomarker for the susceptibility to HCC.[18] *LEPR* rs6588147 G>A is an intron SNP. Slattery et al found this SNP caused colon cancer susceptibility among men.[19]

In view of these previous studies, we found that the relationship of *LEP* and *LEPR* polymorphisms with the development of cancer was unclear, especially in Asians.[20] In this study, we selected the *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A SNPs and conducted a case–control study to determine the relationship between *LEP* and *LEPR* polymorphisms and HCC risk in Eastern Chinese Han population.

Patients and methods

Subjects

This case–control study was performed on two groups. The patient group consisted of 584 HCC cases (mean age 53.17±11.76 years) who were selected from the Department of Hepatobiliary Surgery at Fuzong Clinical Medical College (Fuzhou city, China) and Union Clinical Medical College (Fuzhou city, China) of Fujian Medical University through 2002–2016. HCC diagnosis was confirmed by pathology. Two hepatobiliary surgeons independently evaluated the disease stage according to the criteria of Barcelona Clinic Liver Cancer (2010). The control group consisted of 923 cancer-free participants (mean age 53.72±9.97 years). Written informed consent was signed by each participant included in this study. Approval from the Ethics Committee of Fujian Medical University was obtained. Each participant donated a blood sample which was stored in an EDTA vacutainer tube.

DNA extraction and genotyping

The blood sample obtained from each participant was stored at −80°C immediately. Promega Genomic DNA Kit (Promega Corporation, Fitchburg, WI, USA) was used to extract and purify genomic DNA from lymphocytes. Purity and concentration of genomic DNA were determined by the NanoDrop ND-1000 spectrophotometer and 1.5% agarose gel electrophoresis. SNPscan™ genotyping method (Genesky Biotechologies Inc., Shanghai, China) was used to determine *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A genotypes. Sixty sample sizes (4%) were randomly selected for quality control. The genotyping was performed by our technicians and the results were not changed.

Statistical analysis

Data were analyzed by using SAS 9.4 software (SAS Institute, Cary, NC, USA). Continuous variables were expressed as mean±SD. Student's *t*-test was used to assess the differences in age distribution. Chi-square (χ^2) or Fisher's exact test was used to assess the distribution of age, sex, chronic HBV infection status, smoking status, alcohol use, and genotypes. The deviation from Hardy–Weinberg equilibrium in the control group was determined by using an online calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl)[21–25] to compare the observed genotype frequencies of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A SNPs with the expected frequencies. Using additive, homozygote, dominant, and recessive models, the associations between *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A SNPs and susceptibility of HCC were assessed by crude/adjusted odds ratios (ORs) and confidence intervals (CIs). A $P<0.05$ (two-tailed) was considered as the threshold for statistical significance. In this study, a Bonferroni correction method was used for multiple testing.[26,27]

Results

Baseline characteristics

There were 584 HCC cases and 923 cancer-free controls included in our study. The frequency distributions for age,

Table 1 Distribution of selected demographic variables and risk factors in HCC cases and controls

Variables	Cases (n=584)		Controls (n=923)		*P*-value[a]
	n	%	n	%	
Age (years)	53.17 (±11.76)		53.72 (±9.97)		0.327
Age (years)					0.358
<53	264	45.21	395	42.80	
≥53	320	54.79	528	57.20	
Sex					0.717
Male	525	89.90	835	90.47	
Female	59	10.10	88	9.53	
Smoking status					0.834
Never	374	64.04	596	64.57	
Ever	210	35.96	327	35.43	
Alcohol use					<0.001
Never	414	70.89	775	83.97	
Ever	170	29.11	148	16.03	
Chronic HBV infection					<0.001
Yes	412	70.55	85	9.21	
No	172	29.45	838	90.79	
BCLC classification					
A	392	67.12			
B	175	29.97			
C	17	2.91			

Note: [a]Two-sided χ^2-test and Student's *t*-test.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

sex, chronic HBV infection status, smoking, and alcohol use among HCC patients and controls are summarized in Table 1. The characteristics of HCC cases and controls were fully matched by age and sex. The locus information of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms is shown in Table 2. The genotyping success rate for all SNPs was eligible (>99%). Minor allele frequency of these SNPs was similar to the data of Chinese population. For these included SNPs, the genotype distribution in controls conformed to Hardy–Weinberg equilibrium.

Association of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms with the risk of HCC

Table 3 lists the genotype distribution of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms.

Frequencies of *LEP* rs7799039 AA, AG, and GG genotypes were 51.30%, 38.43%, and 10.26% in HCC cases and 54.83%, 39.09%, and 6.08% in controls, respectively. When compared with the frequency of *LEP* rs7799039 AA genotype, a significant difference was found in the frequency of *LEP* rs7799039 GG genotype between HCC cases and controls (crude OR=1.76, 95% CI, 1.19–2.60, *P*=0.005). When compared with frequency of *LEP* rs7799039 AA/AG genotype, there was a difference in the frequency of *LEP* rs7799039 GG genotype between HCC patients and controls (crude OR=1.77, 95% CI, 1.21–2.59, *P*=0.004). Adjustments for age, sex, chronic HBV infection status, smoking, and drinking, this association was not essentially changed (GG vs AA: adjusted OR=2.03, 95% CI, 1.22–3.38, *P*=0.006 and GG vs AA/AG: adjusted OR=1.97, 95% CI, 1.20–3.22, *P*=0.007; Table 3).

Frequencies of *LEP* rs2167270 GG, GA, and AA genotypes were 59.65%, 34.43%, and 5.91% in HCC patients and 61.24%, 34.85%, and 3.91% in controls, respectively. The association between *LEP* rs2167270 G>A polymorphism and a tendency for increased HCC risk was noted (AA vs GG: crude OR=1.52, 95% CI, 0.93–2.47, *P*=0.093 and AA vs GG/GA: crude OR=1.55, 95% CI, 0.96–2.50, *P*=0.076). Adjustments for age, sex, chronic HBV infection status, smoking, and drinking, this association was more significant (AA vs GG: adjusted OR=2.03, 95% CI, 1.10–3.75, *P*=0.024 and AA vs GG/GA: adjusted OR=2.01, 95% CI, 1.10–3.68, *P*=0.023; Table 3).

Frequencies of *LEPR* rs6588147 GG, GA, and AA genotypes were 77.22%, 21.39%, and 1.39% in HCC patients and 71.77%, 26.71%, and 1.52% in controls, respectively.

Table 2 Primary information for *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms

Genotyped SNPs	Chromosome	Chr Pos (NCBI Build 37)	Region	MAF for Chinese in database	MAF in our controls (n=923)	*P*-value for HWE test in our controls	Genotyping method	Genotyping value (%)
LEP rs7799039 A>G	7	127878783	Promoter	0.201	0.256	0.439	SNPscan	99.27
LEP rs2167270 G>A	7	127881349	5′ UTR	0.175	0.213	0.245	SNPscan	99.27
LEPR rs1137100 G>A	1	66036441	Exon 4	0.169	0.155	0.203	SNPscan	99.27
LEPR rs1137101 G>A	1	66058513	Exon 6	0.111	0.116	0.453	SNPscan	99.20
LEPR rs6588147 G>A	1	65935494	Intron 2	0.150	0.149	0.097	SNPscan	99.27

Abbreviations: HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; UTR, untranslated region.

Table 3 Logistic regression analyses of association between *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A SNPs and the risk of HCC

Genotype	Cases (n=584)		Controls (n=923)		Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
	n	%	n	%				
LEP rs7799039 A>G								
AA	295	51.30	505	54.83	1.00		1.00	
AG	221	38.43	360	39.09	1.02 (0.82–1.28)	0.834	1.11 (0.83–1.48)	0.498
GG	59	10.26	56	6.08	**1.76 (1.19–2.60)**	**0.005**	**2.03 (1.22–3.38)**	**0.006**
AG+GG	280	48.70	416	45.17	1.15 (0.94–1.42)	0.183	1.25 (0.95–1.65)	0.110
AA+AG	516	89.74	865	93.92	1.00		1.00	
GG	59	10.26	56	6.08	**1.77 (1.21–2.59)**	**0.004**	**1.97 (1.20–3.22)**	**0.007**
G allele	339	29.48	472	25.62				
LEP rs2167270 G>A								
GG	343	59.65	564	61.24	1.00		1.00	
GA	198	34.43	321	34.85	0.99 (0.80–1.24)	0.942	1.04 (0.78–1.40)	0.774
AA	34	5.91	36	3.91	1.52 (0.93–2.47)	0.093	**2.03 (1.10–3.75)**	**0.024**
GA+AA	232	40.35	357	38.76	1.07 (0.86–1.32)	0.541	1.15 (0.87–1.53)	0.316
GG+GA	541	94.09	885	96.09	1.00		1.00	
AA	34	5.91	36	3.91	1.55 (0.96–2.50)	0.076	**2.01 (1.10–3.68)**	**0.023**
A allele	266	23.13	393	21.34				
LEPR rs6588147 G>A								
GG	444	77.22	661	71.77	1.00		1.00	
GA	123	21.39	246	26.71	**0.73 (0.57–0.94)**	**0.013**	**0.62 (0.45–0.86)**	**0.005**
AA	8	1.39	14	1.52	0.84 (0.35–2.01)	0.690	0.85 (0.27–2.69)	0.777
GA+AA	131	22.78	260	28.23	**0.75 (0.59–0.96)**	**0.020**	**0.64 (0.47–0.88)**	**0.007**
GG+GA	567	98.61	907	98.48	1.00		1.00	
AA	8	1.39	14	1.52	0.92 (0.38–2.20)	0.842	0.96 (0.31–3.03)	0.947
A allele	139	12.09	274	14.88				
LEPR rs1137100 G>A								
GG	424	73.74	653	70.90	1.00		1.00	
GA	143	24.87	251	27.25	0.86 (0.68–1.09)	0.222	0.75 (0.55–1.03)	0.074
AA	8	1.39	17	1.85	0.71 (0.31–1.66)	0.433	0.62 (0.20–1.92)	0.408
GA+AA	151	26.26	268	29.10	0.87 (0.69–1.10)	0.235	0.75 (0.55–1.02)	0.069
GG+GA	567	98.61	904	98.15	1.00		1.00	
AA	8	1.39	17	1.85	0.75 (0.32–1.75)	0.506	0.68 (0.22–2.07)	0.496
A allele	159	27.65	285	15.47				
LEPR rs1137101 G>A								
GG	453	78.78	717	77.93	1.00		1.00	
GA	119	20.70	193	20.98	0.96 (0.74–1.24)	0.761	0.81 (0.58–1.14)	0.230
AA	3	0.52	10	1.09	0.47 (0.13–1.71)	0.251	0.22 (0.05–1.10)	0.065
GA+AA	122	21.22	203	22.07	0.95 (0.74–1.23)	0.700	0.78 (0.56–1.09)	0.152
GG+GA	572	99.48	910	98.91	1.00		1.00	
AA	3	0.52	10	1.09	0.48 (0.13–1.74)	0.264	0.24 (0.05–1.16)	0.076
A allele	125	10.87	213	11.58				

Notes: [a]Adjusted for age, sex, smoking status, alcohol use, and chronic HBV infection status. Bold values are statistically significant ($P<0.05$).
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LEP, leptin; LEPR, LEP receptor; OR, odds ratio; SNPs, single-nucleotide polymorphisms.

When compared with the frequency of *LEPR* rs6588147 GG genotype, a significant difference was found in the frequency of *LEPR* rs6588147 GA genotype between HCC cases and controls (crude OR=0.73, 95% CI, 0.57–0.94, *P*=0.013). When compared with the frequency of *LEPR* rs6588147 GG genotype, there was a difference in the frequency of *LEPR* rs6588147 GA/AA genotype between HCC patients and controls (crude OR=0.75, 95% CI, 0.59–0.96, *P*=0.020). Adjustments for age, sex, chronic HBV infection status, smoking, and drinking, this association was more significant (GA vs GG: adjusted OR=0.62, 95% CI, 0.45–0.86, *P*=0.005 and AA/GA vs GG: adjusted OR=0.64; 95% CI, 0.47–0.88, *P*=0.007; Table 3).

However, we found no association between *LEPR* rs1137100 G>A and rs1137101 G>A polymorphisms and the risk of HCC in any genetic model (Table 3).

We used Bonferroni correction method to conduct a multiple testing. We found the genotype distribution of *LEP* rs7799039 A>G and *LEPR* rs6588147 G>A SNPs was still significantly different between HCC patients and cancer-free controls (P=0.006 and 0.007 for *LEP* rs7799039 A>G, and P=0.005 and 0.007 for *LEPR* rs6588147 G>A, respectively).

Discussion

Although chronic HBV infection status is associated with the etiology of HCC, the individual's hereditary factor may influence the susceptibility to HCC. Recently, it is believed that the metabolic disturbance increases the susceptibility to many malignancies.[4] Thus, the metabolism-related gene may affect the development of HCC. In this case–control study, we explored the relationship of *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms with the risk of HCC in 584 patients and 923 control subjects in Eastern Chinese Han population. We found that *LEP* rs7799039 A>G and rs2167270 G>A polymorphisms were associated with the susceptibility of HCC in this population. However, *LEPR* rs6588147 G>A polymorphism decreased the risk of HCC. To our knowledge, this is the study with the largest sample size on the relationship between *LEP* rs2167270 G>A, rs7799039 A>G, *LEPR* rs6588147 G>A, rs1137100 G>A, and rs1137101 G>A polymorphisms and HCC risk.

LEP rs7799039 A>G is a promoter SNP, which was suggested it could affect transcriptional level and LEP expression.[14] In this study, we found that *LEP* rs7799039 A>G polymorphism was associated with the susceptibility to HCC in Chinese Han population. Recently, a meta-analysis which included 16 published studies of 6,569 cancer cases and 8,405 controls demonstrated that *LEP* rs7799039 A>G polymorphism may decrease the risk of cancer.[20] In addition, this association between *LEP* rs7799039 A>G polymorphism and cancer risk was also found in other meta-analyses.[16,17] However, the association between *LEP* rs7799039 A>G polymorphism and the risk of cancer was seldom studied in Asian populations. Clearly, these ambiguous findings suggested that the functions of *LEP* rs7799039 A>G variants might be different in different races. It was found that the minor allele frequency of *LEP* rs7799039 A>G polymorphism might alter sharply among different populations (0.201 [Chinese] vs 0.597 [Caucasians]).[28] Recently, Romanowski et al reported that *LEP* rs2167270 G>A polymorphism increased the risk of posttransplant diabetes mellitus.[29] *LEP* rs2167270 G>A is located in 5′-untranslated region and may influence the translation process of *LEP* mRNA. A functional study demonstrated that serum LEP concentrations in *LEP* rs2167270 GA genotype were higher than in individuals with rs2167270 GG genotype.[30] In this study, the association between *LEP* rs2167270 G>A polymorphism and increased risk of HCC was found, which was very similar to the findings of the previous meta-analysis.[15] In the future, more case–control studies should be carried out to explore the potential association of *LEP* rs7799039 A>G and *LEP* rs2167270 G>A polymorphisms with cancer risk in Asians.

Slattery et al reported that *LEPR* rs6588147 AA genotype had a tendency to lower susceptibility of colon cancer in a mixed population.[19] We found that rs6588147 A allele may be associated with the decreased susceptibility of HCC, which was similar to previous findings. In our study, after Bonferroni correction test, this association was still significant between HCC patients and cancer-free controls. However, Nyante et al identified that the *LEPR* rs6588147 G>A polymorphism might confer susceptibility to breast cancer in luminal A subtype.[31] Only a few investigations focused on the correlation between *LEPR* rs6588147 G>A polymorphism and the risk of cancer, especially in Asians. In future, the association of this SNP with cancer susceptibility should be further studied with a large sample size. Also, functional studies are needed to identify the real biologic function of *LEPR* rs6588147 G>A polymorphism on the development of HCC.

There are some limitations in this study. First, since the number of HCC cases and controls was moderate, the power of study might be limited. Second, the HCC cases and controls were both enrolled from local hospitals. Therefore, selection bias should have occurred. Third, for lack of some important data, such as lifestyle, dietary habits, and environmental carcinogens exposure, the interaction of gene–environment was not studied. Fourth, the information available on HCC survival has been insufficient till now; thus, we could not further analyze the potential role of *LEP*/*LEPR* functional polymorphisms in HCC progression and prognosis. Fifth, due to lack of sufficient information on height and weight, the body mass index was not considered in this study. Finally, we only selected some functional SNPs in *LEP* and *LEPR* genes, and a fine-mapping or Genome Wide Association study focusing on *LEP* and *LEPR* genes should be performed to further explore the potential relationship of *LEP* and *LEPR* SNPs with the risk of HCC.

To sum up, this study has demonstrated that *LEP* rs7799039 A>G and rs2167270 G>A polymorphisms are genetic risk factors for HCC with various degrees of

relationship in an Eastern Chinese Han population. However, *LEPR* rs6588147 G>A may decrease the risk of HCC. Further epidemiologic case–control studies are needed to assess the interaction of *LEP* and *LEPR* genotypes with the exposure to environmental carcinogens, lifestyle, and dietary habits.

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Disclosure

The authors report no conflicts of interest in this work.

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