

Relationship of *PPARG*, *PPARGC1A*, and *PPARGC1B* polymorphisms with susceptibility to hepatocellular carcinoma in an eastern Chinese Han population

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Background: *PPARG*, *PPARGC1A*, and *PPARGC1B* polymorphisms may be implicated in the development of cancer.

Participants and methods: In this study, we selected *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A single-nucleotide polymorphisms to explore the relationship between these polymorphisms and hepatocellular carcinoma (HCC) risk. A total of 584 HCC patients and 923 controls were enrolled.

Results: We found that *PPARG* rs1801282 C>G polymorphism was correlated with a decreased susceptibility of HCC (CG vs CC, adjusted OR 0.47, 95% CI 0.27–0.82, $P=0.007$; CG/GG vs CC, adjusted OR 0.52, 95% CI 0.31–0.88, $P=0.015$). However, *PPARG* rs3856806 C>T polymorphism was a risk factor for HCC (TT vs CC, adjusted OR 2.33, 95% CI 1.25–4.36, $P=0.008$; TT vs CT/CC, adjusted OR 2.26, 95% CI 1.22–4.17, $P=0.010$). In a subgroup analysis by chronic hepatitis B virus (HBV)-infection status, age, sex, alcohol use, and smoking status, a significant association between *PPARG* rs1801282 C>G polymorphism and a decreased risk of HCC in male, ≥ 53 years, never-smoking, never-drinking, and nonchronic HBV-infection-status subgroups was found. However, we found *PPARG* rs3856806 C>T polymorphism increased the risk of HCC in never-smoking, never-drinking, and nonchronic HBV-infection-status subgroups. Haplotype-comparison analysis indicated that C_{rs1801282}T_{rs3856806}C_{rs2970847}G_{rs7732671}G_{rs17572019} and C_{rs1801282}T_{rs3856806}T_{rs2970847}G_{rs7732671}G_{rs17572019} haplotypes increased the risk of HCC. *PPARG* C_{rs1801282}T_{rs3856806} and G_{rs1801282}C_{rs3856806} haplotypes also influenced the risk of HCC.

Conclusion: In conclusion, our findings suggest *PPARG* polymorphisms may influence the susceptibility of HCC. The *PPARG*, *PPARGC1A*, and *PPARGC1B* haplotypes might be associated with HCC risk.

Keywords: *PPARG*, *PPARGC1A*, *PPARGC1B*, polymorphism, risk, hepatitis B virus, hepatocellular carcinoma

Introduction

In 2012, an estimated 782,500 new liver cancer (LC) patients and 745,500 related deaths occurred worldwide.¹ China accounts for almost half the total number of LC cases and deaths annually. Hepatocellular carcinoma (HCC) is the most common subtype of LC. A large number of HCC cases are diagnosed annually, with a high mortality rate, which encourages people to explore the potential risk factors for HCC. Due to the chronic infection of hepatitis B virus (HBV), the incidence of HCC in parts of sub-Saharan Africa and Asia is much higher than other regions.^{2,3} However, other

risk factors might also contribute to the etiology of HCC. Recently, many hereditary factors have been found to confer susceptibility to HCC.

Peroxisome proliferator-activated receptors (PPARs), a cluster of important nuclear transcription factors, may be involved in the process of cellular differentiation and regulate carbohydrate/lipid metabolism and energy balance.⁴ There are three predominant subtypes in PPARs: PPAR α , PPAR β , and PPAR γ .⁵ PPAR γ , also known as PPARG, is located on chromosome 3p25. PPARG interacts with RXR and forms a dipolymer to regulate its target genes, which are involved in adipocyte differentiation and insulin sensitization.⁶ It has been reported that PPARG possessed anti-inflammatory roles^{7,8} and can restrain the production of many inflammatory mediators, such as IL6, IL8, and TNF α .⁹ Several studies have found that obesity, metabolic syndrome, insulin resistance/insufficiency, type 2 diabetes mellitus (T2DM), and inflammation have a common molecular basis, in which PPARG can influence the process of these diseases and might alter the risk of cancer.^{10–12} Two coactivators of PPARG, PPARGC1A and PPARGC1B, are vital regulators of energy metabolism.¹³ In addition, Li et al reported that PPARGC1A might be a potential biomarker for lung cancer prognosis.¹⁴ Eichner et al found that miR378 was embedded within *PPARGC1B*, which encodes PPARGC1B, and miR378 expression correlated with progression of breast cancer in humans.¹⁵

Recently, a meta-analysis found that *PPARG* rs1801282 C>G single-nucleotide polymorphism (SNP) was associated with cancer risk in Asians;¹⁶ however, the studies included were limited.¹⁶ *PPARG* rs3856806 C>T polymorphism is believed to be related to inflammatory response¹⁷ and is associated with the development of ovarian carcinoma,¹⁸ follicular lymphoma,¹⁹ and colorectal cancer.^{20–22} Studies have reported that *PPARGC1A* rs2970847 C>T SNP increased the risk of T2DM.^{23,24} However, the association between this SNP and cancer risk is unknown. Martínez-Nava et al studied the association of *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs with risk of breast cancer and found that the *PPARGC1B* rs7732671 C allele was a protective factor for breast cancer.²⁵ In view of these previous studies, the potential role of *PPARG*, *PPARGC1A*, and *PPARGC1B* SNPs in determining HCC risk was unclear. Understanding the possible relationship might be beneficial for HCC prevention. Therefore, in this case-control study, we selected *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs to explore the relationship between these polymorphisms and HCC risk in an eastern Chinese Han population.

Participants and methods

Subjects

As part of an ongoing study carried out in an eastern Chinese Han population, the first 584 incident HCC patients and 923 hospital-based controls were recruited in this study. Our case-control study was approved by Fujian Medical University Ethics Committee (Fuzhou, China). HCC cases were recruited from the Department of Hepatobiliary Surgery at Fuzong Clinical Medical College and Union Clinical Medical College of Fujian Medical University. All HCC patients were diagnosed by pathology. Major selection criteria of HCC patients were sporadic HCC cases, HCC patients without chemoradiotherapy, Chinese Han population, and living in eastern China. Corresponding exclusion criteria were HCC patients with autoimmune disease history, had received prior chemoradiotherapy, had other malignancy history, and without a pathological diagnosis. Meanwhile, a total of 923 participants who attended a physical examination in the hospitals mentioned were enrolled as controls. Additionally, criteria for control selection were healthy subjects without a history of malignancy, without autoimmune disease, without chronic liver disease, and eastern Chinese Han. HCC patients and controls matched well by age and sex. All subjects were recruited between January 2002 and December 2016 consecutively. Demographic variables and risk factors (eg, smoking, drinking, and chronic HBV-infection status) were collected by our colleagues. Written informed consent was signed by all subjects. Information is listed in Table 1.

DNA extraction and genotyping

Extraction of genomic DNA from EDTA anticoagulant blood samples was performed using a DNA-purification kit (Promega, Madison, WI, USA). Purity and concentration of the DNA samples obtained was assessed by spectrophotometry with the NanoDrop ND-1000 and 1.5% agarose gel electrophoresis. Genomic DNA was stored at -80°C . Genotyping of *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs was carried out with a genotyping assay (SNPscan; Genesky Biotechnologies, Shanghai, China) on a 3730XL (Thermo Fisher Scientific, Waltham, MA, USA). Data were observed using GeneMapper 4.1 software (Thermo Fisher Scientific). Sixty (4%) randomly selected samples were tested again by a different technologist. The results were not altered.

Statistical analysis

All statistical analyses were done with SAS 9.4 software (SAS Institute, Cary, NC, USA) using Student's *t*-test,

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

Variable	Cases (n=584)		Controls (n=923)		P-value ^a
	n	%	n	%	
Mean 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: ^aTwo-sided χ^2 -test and Student's *t*-test.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Fisher's exact test, and χ^2 -test. Age was expressed as the mean \pm SD. We used Student's *t*-test to determine the differences in age distribution between HCC cases and controls, and χ^2 -test or Fisher's exact test used to assess potential differences in age, sex, smoking status, alcohol use, chronic HBV-infection status, and genotypes. Deviation from Hardy–Weinberg equilibrium (HWE) was determined using an Internet-based calculator (<http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>)^{26,27} to compare the obtained genotype frequencies in controls with the expected

frequencies. Using different models of inheritance (allele, additive, homozygote, dominant, and recessive), associations between *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs and risk of HCC were determined by crude/adjusted ORs and CIs. SHEsis software (Bio-X, Shanghai, China), an online calculator, was used for construction of *PPARG*, *PPARGC1A*, and *PPARGC1B* haplotypes.²⁸ $P<0.05$ (two-tailed) was used as the threshold for significance. In this study, Bonferroni correction was performed for multiple testing.^{29,30} Power and Sample Size Calculation software (<http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize>) was used to assess the statistical power of this study ($\alpha=0.05$).³¹

Results

Baseline characteristics

HCC patients and cancer-free controls comprised 584 and 923 subjects, respectively. Mean ages were 53.17 \pm 11.76 (range 20–83) years in the HCC group and 53.72 \pm 9.97 (range 21–83) years in controls. Baseline characteristics of HCC patients and controls are given in Table 1. In addition, Table 1 shows that our study was well matched by sex and age. Corresponding SNP information for *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A polymorphisms is summarized in Table 2. The success rate of genotyping was >99% (Table 2). The minor-allele frequency in controls is listed in Table 2, and results were similar to the data for Chinese Han population. In controls, except for *PPARG* rs3856806 C>T, the distribution of *PPARG* rs1801282 C>G, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A genotype frequencies accorded with HWE.

Table 2 Primary information for *PPARG* rs1801282 C>G, rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C, rs17572019 G>A polymorphisms

Genotyped SNPs	<i>PPARG</i> rs1801282 C>G	<i>PPARG</i> rs3856806 C>T	<i>PPARGC1A</i> rs2970847 C>T	<i>PPARGC1B</i> rs7732671 G>C	<i>PPARGC1B</i> rs17572019 G>A
Chromosome	3	3	4	5	5
Function	Missense	Coding-synonymous	Coding-synonymous	Missense	Missense
“Chr Pos” (NCBI build 37)	12393125	12475557	23815924	149212243	149212471
MAF for Chinese in database	0.07	0.25	0.28	0.09	0.07
MAF in our controls (n=923)	0.05	0.22	0.22	0.06	0.06
P-value for HWE test in our controls	0.883	0.009	0.498	0.241	0.543
Genotyping method	SNP scan	SNP scan	SNP scan	SNP scan	SNP scan
Percentage genotyping value	99.27%	99.27%	99.27%	99.27%	99.27%

Abbreviations: MAF, minor-allele frequency; HWE, Hardy–Weinberg equilibrium; SNP, single-nucleotide polymorphism.

Association of *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs with HCC

The frequencies of *PPARG* rs1801282 genotypes in HCC patients and controls are summarized in Table 3. We found that the *PPARG* rs1801282 G allele was associated with a decreased risk of HCC (CG vs CC, crude OR 0.47, 95% CI 0.31–0.72, $P=0.001$; CG/GG vs CC, crude OR 0.51, 95% CI 0.34–0.77, $P=0.001$; G vs C, crude OR 0.56, 95% CI 0.38–0.82, $P=0.003$). After adjustments for age, sex, smoking, drinking, and chronic HBV-infection status, the results were not essentially changed (CG vs CC, adjusted OR 0.47, 95% CI 0.27–0.82, $P=0.007$; CG/GG vs CC, adjusted OR 0.52, 95% CI 0.31–0.88, $P=0.015$; Table 3).

Table 3 lists the frequencies of *PPARG* rs3856806 genotypes in HCC patients and controls. We found that the *PPARG* rs3856806 T allele conferred risk to HCC (TT vs CC, crude OR 2.12, 95% CI 1.31–3.44, $P=0.002$; TT vs CC/CT, crude OR 2.13, 95% CI 1.33–3.43, $P=0.002$; T vs C, crude OR 1.21, 95% CI 1.02–1.44, $P=0.029$). After adjustments for age, sex, smoking, drinking, and chronic HBV-infection status, the results were not materially altered (TT vs CC, adjusted OR 2.33, 95% CI 1.25–4.36, $P=0.008$; TT vs CT/CC, adjusted OR 2.26, 95% CI 1.22–4.17, $P=0.010$; Table 3). However, *PPARGC1A* rs2970847 C>T and *PPARGC1B* rs7732671 G>C and rs17572019 G>A polymorphisms were not associated with HCC risk in all genetic models (Table 3).

We performed a Bonferroni correction for multiple testing. The genotype distribution of *PPARG* polymorphisms was still significantly different between HCC cases and controls ($P=0.007$ for rs1801282 C>G, $P=0.008$ and $P=0.010$ for rs3856806 C>T, respectively). We also calculated the statistical power of this study ($\alpha=0.05$) using Power and Sample Size Calculation.³¹ For *PPARG* rs1801282 C>G, the power value was 0.955 in CG vs CC, 0.906 in GG/CG vs CC, and 0.859 in G vs C. For *PPARG* rs3856806 C>T, the power value was 0.932 in TT vs CC, 0.921 in TT vs CC/CT, and 0.584 in T vs C.

Association of *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs with HCC in different subgroups

Table 4 shows the relationship of *PPARG* rs1801282 C>G polymorphism with risk of HCC in the stratified analyses.

After adjustment by logistic regression analysis, we found that the *PPARG* rs1801282 G allele decreased the risk of HCC (male subgroup, CG vs CC, adjusted OR 0.52, 95% CI 0.29–0.92, $P=0.025$ and CG/GG vs CC, adjusted OR 0.52, 95% CI 0.29–0.91, $P=0.022$; ≥ 53 years subgroup, CG vs CC, adjusted OR 0.36, 95% CI 0.17–0.74, $P=0.006$ and CG/GG vs CC, adjusted OR 0.38, 95% CI 0.19–0.77, $P=0.007$; never-smoking subgroup, CG vs CC, adjusted OR 0.32, 95% CI 0.15–0.66, $P=0.002$ and CG/GG vs CC, adjusted OR 0.39, 95% CI 0.20–0.77, $P=0.007$; never-drinking subgroup, CG vs CC, adjusted OR 0.40, 95% CI 0.21–0.76, $P=0.005$ and CG/GG vs CC, adjusted OR 0.47, 95% CI 0.26–0.86, $P=0.015$; nonchronic HBV-infection subgroup, CG vs CC, adjusted OR 0.42, 95% CI 0.20–0.89, $P=0.024$ and CG/GG vs CC, adjusted OR 0.46, 95% CI 0.22–0.93, $P=0.030$).

As listed in Table 5, we found that the *PPARG* rs3856806 T allele was associated with a risk of HCC in some subgroups (never-smoking subgroup, TT vs CC, adjusted OR 2.24, 95% CI 1.09–4.60, $P=0.028$ and TT vs CT/CC, adjusted OR 2.21, 95% CI 1.09–4.49, $P=0.027$; never-drinking subgroup, TT vs CC, adjusted OR 2.10, 95% CI 1.05–4.19, $P=0.036$ and TT vs CT/CC, adjusted OR 2.08, 95% CI 1.05–4.11, $P=0.035$; nonchronic HBV-infection subgroup, TT vs CC, adjusted OR 2.44, 95% CI 1.22–4.88, $P=0.012$ and TT vs CT/CC, adjusted OR 2.34, 95% CI 1.19–4.60, $P=0.014$). However, *PPARGC1A* rs2970847 C>T and *PPARGC1B* rs7732671 G>C and rs17572019 G>A polymorphisms were not associated with HCC risk in any subgroup (data not shown).

SNP haplotypes

Using the SHESIS online calculator,²⁸ we constructed several haplotypes of *PPARG*, *PPARGC1A*, and *PPARGC1B* genes (Table 6). Haplotype comparison analysis indicated that $C_{rs1801282}T_{rs3856806}C_{rs2970847}G_{rs7732671}G_{rs17572019}$, $C_{rs1801282}T_{rs3856806}T_{rs2970847}G_{rs7732671}G_{rs17572019}$, and $C_{rs1801282}C_{rs3856806}C_{rs2970847}C_{rs7732671}A_{rs17572019}$ were associated with risk of HCC (OR 1.29, 95% CI 1.05–1.59, $P=0.017$; OR 1.56, 95% CI 1.08–2.25, $P=0.017$; and OR 1.63, 95% CI 1.11–2.39, $P=0.011$, respectively). In addition, *PPARG* $C_{rs1801282}T_{rs3856806}$ and $G_{rs1801282}C_{rs3856806}$ haplotypes also influenced the risk of HCC (OR 1.31, 95% CI 1.09–1.57, $P=0.004$ and OR 0.46, 95% CI 0.21–1.00, $P=0.046$, respectively).

Discussion

PPARG, *PPARGC1A*, and *PPARGC1B* genes may have an impact on inflammatory response, insulin sensitization, cell differentiation, and cellular apoptosis^{32–35} and alter the risk of cancer. In this study, we examined the relationship between *PPARG* rs1801282 C>G and rs3856806 C>T,

Table 3 Logistic regression analyses of associations between *PPARG* rs1801282 C>G, rs3856806 C>T, *PPARGC1A* rs2970847 C>T, and *PPARGC1B* rs7732671 G>C, rs17572019 G>A polymorphisms and risk of HCC

Genotype	HCC cases (n=584)		Controls (n=923)		Crude OR (95% CI)	P-value	Adjusted OR ^a (95% CI)	P-value
	n	%	n	%				
<i>PPARG</i> rs1801282 C>G								
CC	542	94.26	823	89.36	1.00		1.00	
CG	30	5.22	95	10.31	0.47 (0.31–0.72)	0.001	0.47 (0.27–0.82)	0.007
GG	3	0.52	3	0.33	1.50 (0.30–7.45)	0.622	1.97 (0.28–14.13)	0.500
GC + GG	33	5.74	98	10.64	0.51 (0.34–0.77)	0.001	0.52 (0.31–0.88)	0.015
CC + GC	572	99.48	918	99.67	1.00		1.00	
GG	3	0.52	3	0.33	1.61 (0.32–7.98)	0.563	2.07 (0.29–14.86)	0.467
C allele	1,114	96.87	1,741	94.52	1.00			
G allele	36	3.13	101	5.48	0.56 (0.38–0.82)	0.003		
<i>PPARG</i> rs3856806 C>T								
CC	320	55.65	543	58.96	1.00		1.00	
CT	214	37.22	346	37.57	1.03 (0.82–1.28)	0.828	1.11 (0.83–1.48)	0.483
TT	41	7.13	32	3.47	2.12 (1.31–3.44)	0.002	2.33 (1.25–4.36)	0.008
CT + TT	255	44.35	378	41.04	1.15 (0.93–1.41)	0.208	1.23 (0.93–1.62)	0.145
CC + CT	534	92.87	889	96.53	1.00		1.00	
TT	41	7.13	32	3.47	2.13 (1.33–3.43)	0.002	2.26 (1.22–4.17)	0.010
C allele	854	74.26	1,432	77.74	1.00			
T allele	296	25.74	410	22.26	1.21 (1.02–1.44)	0.029		
<i>PPARGC1A</i> rs2970847 C>T								
CC	356	61.91	557	60.48	1.00		1.00	
CT	194	33.74	323	35.07	0.92 (0.74–1.15)	0.460	0.98 (0.73–1.31)	0.869
TT	25	4.35	41	4.45	0.93 (0.56–1.56)	0.794	1.25 (0.64–2.43)	0.520
CT + TT	219	38.09	364	39.52	0.94 (0.76–1.17)	0.580	1.02 (0.77–1.35)	0.907
CC + CT	550	95.65	880	95.55	1.00		1.00	
TT	25	4.35	41	4.45	0.98 (0.59–1.62)	0.924	1.27 (0.65–2.45)	0.483
C allele	906	78.78	1,437	78.01	1.00			
T allele	244	21.22	405	21.99	0.96 (0.80–1.14)	0.619		
<i>PPARGC1B</i> rs7732671 G>C								
GG	497	86.43	819	88.93	1.00		1.00	
GC	77	13.39	101	10.97	1.24 (0.90–1.70)	0.188	1.27 (0.83–1.94)	0.275
CC	1	0.17	1	0.11	1.62 (0.10–26.00)	0.732	1.07 (0.02–49.52)	0.971
GC + CC	78	13.57	102	11.07	1.26 (0.92–1.73)	0.150	1.28 (0.84–1.95)	0.256
GG + GC	574	99.83	920	99.89	1.00		1.00	
CC	1	0.17	1	0.11	1.60 (0.10–25.68)	0.739	1.06 (0.02–48.26)	0.977
G allele	1,071	93.13	1,739	94.41	1.00			
C allele	79	6.87	103	5.59	1.25 (0.92–1.69)	0.155		
<i>PPARGC1B</i> rs17572019 G>A								
GG	496	86.26	818	88.82	1.00		1.00	
GA	78	13.57	101	10.97	1.25 (0.92–1.72)	0.160	1.27 (0.83–1.94)	0.268
AA	1	0.17	2	0.22	0.81 (0.07–8.98)	0.865	0.78 (0.03–22.31)	0.885
GA + AA	79	13.74	103	11.18	1.27 (0.92–1.73)	0.142	1.28 (0.84–1.94)	0.258
GG + GA	574	99.83	919	99.78	1.00		1.00	
AA	1	0.17	2	0.22	0.80 (0.07–8.85)	0.856	0.77 (0.03–21.71)	0.876
G allele	1,070	93.04	1,737	94.30	1.00			
A allele	80	6.96	105	5.70	1.24 (0.92–1.67)	0.165		

Notes: ^aAdjusted for age, sex, smoking status, alcohol use, and chronic HBV infection status. Bold represents statistically significant values ($P < 0.05$).

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus.

PPARGC1A rs2970847 C>T, and *PPARGC1B* rs7732671 G>C and rs17572019 G>A SNPs and HCC risk. We found that *PPARG* rs1801282 C>G polymorphism decreased the risk of HCC. However, *PPARG* rs3856806 C>T was a risk factor for HCC. In subgroup analyses, we found that the

PPARG rs1801282 C>G polymorphism decreased the risk of HCC in male, ≥ 53 years, never-smoking, never-drinking, and nonchronic HBV-infection-status subgroups. However, *PPARG* rs3856806 C>T polymorphism increased the risk of HCC in never-smoking, never-drinking, and nonchronic

Table 4 Stratified analyses between *PPARG* rs1801282 C>G polymorphism and HCC risk by chronic HBV infection, sex, age, smoking status, and alcohol consumption

	Case/control ^a				Adjusted OR ^b (95% CI), P-value				
	CC	GC	GG	GC/GG	CC	GC	GG	GC/GG	GG vs (GC/CC)
Sex									
Male	486/741	30/89	1/3	31/92	1.00	0.52 (0.29–0.92), P=0.025	0.37 (0.02–6.53), P=0.498	0.52 (0.29–0.91), P=0.022	0.39 (0.02–6.88), P=0.523
Female	56/82	0/6	2/0	2/6	1.00	–	–	0.67 (0.12–3.82), P=0.651	–
Age (years)									
<53	244/360	14/31	2/2	16/33	1.00	0.69 (0.29–1.62), P=0.389	3.07 (0.29–32.72), P=0.352	0.80 (0.36–1.81), P=0.595	3.16 (0.30–33.49), P=0.339
≥53	298/463	16/64	1/1	17/65	1.00	0.36 (0.17–0.74), P=0.006	1.09 (0.03–40.25), P=0.961	0.38 (0.19–0.77), P=0.007	1.19 (0.03–43.65), P=0.924
Smoking status									
Never	350/532	15/59	3/3	18/62	1.00	0.32 (0.15–0.66), P=0.002	2.08 (0.30–14.42), P=0.459	0.39 (0.20–0.77), P=0.007	2.21 (0.32–15.24), P=0.421
Ever	192/291	15/36	0/0	15/36	1.00	0.87 (0.37–2.04), P=0.743	–	0.87 (0.37–2.04), P=0.743	–
Alcohol use									
Never	386/692	19/79	3/2	22/81	1.00	0.40 (0.21–0.76), P=0.005	3.43 (0.40–29.32), P=0.261	0.47 (0.26–0.86), P=0.015	3.64 (0.43–30.96), P=0.238
Ever	156/131	11/16	0/1	11/17	1.00	0.79 (0.26–2.35), P=0.667	–	0.75 (0.26–2.22), P=0.607	–
Chronic HBV infection									
Yes	380/78	22/7	2/0	24/7	1.00	0.53 (0.21–1.35), P=0.180	–	0.64 (0.25–1.61), P=0.338	–
No	162/745	8/88	1/3	9/91	1.00	0.42 (0.20–0.89), P=0.024	1.22 (0.12–12.21), P=0.867	0.46 (0.22–0.93), P=0.030	1.29 (0.13–12.89), P=0.832

Notes: ^aGenotyping successful in 584 (98.46%) HCC cases and 923 (99.78%) controls for *PPARG* rs1801282 C>G; ^badjusted for age, sex, smoking status, chronic HBV infection, and alcohol use (besides stratified factors accordingly) in a logistic regression model. Bold represents statistically significant values (P<0.05).

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus.

Table 5 Stratified analyses between *PPARG* rs3856806 C>T polymorphism and HCC risk by chronic HBV infection, sex, age, smoking status, and alcohol consumption

	Case/control ^a				Adjusted OR ^b (95% CI), P-value				
	CC	CT	TT	CT/TT	CC	CT	TT	CT/TT	TT vs (CT/CC)
Sex									
Male	285/491	196/315	36/27	232/342	1.00	1.08 (0.79–1.48), P=0.635	1.89 (0.94–3.81), P=0.074	1.17 (0.86–1.58), P=0.317	1.85 (0.93–3.69), P=0.078
Female	35/52	18/31	5/5	23/36	1.00	1.06 (0.45–2.50), P=0.888	3.99 (0.91–17.44), P=0.066	1.38 (0.62–3.07), P=0.437	3.95 (0.95–16.47), P=0.059
Age (years)									
<53	143/230	99/150	18/13	117/163	1.00	1.25 (0.81–1.92), P=0.320	2.30 (0.85–6.20), P=0.100	1.36 (0.89–2.07), P=0.153	2.13 (0.80–5.63), P=0.129
≥53	177/313	115/196	23/19	138/215	1.00	1.00 (0.68–1.47), P=0.982	2.21 (0.97–5.01), P=0.058	1.11 (0.77–1.61), P=0.577	2.23 (1.00–4.97), P=0.051
Smoking status									
Never	204/347	137/222	27/25	164/247	1.00	1.06 (0.75–1.50), P=0.757	2.24 (1.09–4.60), P=0.028	1.19 (0.85–1.65), P=0.317	2.21 (1.09–4.49), P=0.027
Ever	116/196	77/124	14/7	91/131	1.00	1.27 (0.75–2.16), P=0.379	2.78 (0.73–10.55), P=0.133	1.38 (0.82–2.30), P=0.226	2.53 (0.8–9.38), P=0.164
Alcohol use									
Never	230/457	149/288	29/28	178/316	1.00	1.05 (0.76–1.44), P=0.779	2.10 (1.05–4.19), P=0.036	1.16 (0.85–1.58), P=0.350	2.08 (1.05–4.11), P=0.035
Ever	90/86	65/58	12/4	77/62	1.00	1.39 (0.72–2.67), P=0.328	3.57 (0.84–15.10), P=0.085	1.54 (0.82–2.91), P=0.178	3.10 (0.76–12.70), P=0.116
Chronic HBV infection									
Yes	230/52	147/29	27/4	174/33	1.00	1.01 (0.60–1.71), P=0.971	1.24 (0.40–3.85), P=0.712	1.07 (0.65–1.78), P=0.787	1.26 (0.41–3.84), P=0.686
No	90/491	67/317	14/28	81/345	1.00	1.12 (0.79–1.59), P=0.523	2.44 (1.22–4.88), P=0.012	1.24 (0.89–1.74), P=0.203	2.34 (1.19–4.60), P=0.014

Notes: ^aGenotyping successful in 584 (98.46%) HCC cases and 923 (99.78%) controls for *PPARG* rs3856806 C>T; ^badjusted for age, sex, smoking status, chronic HBV infection, and alcohol use (besides stratified factors accordingly) in a logistic regression model. Bold represents statistically significant values (P<0.05).

Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus.

Table 6 PPARG, PPARGC1A, PPARGC1B haplotype frequency (%) in cases and controls and HCC risk

	Cases n (%)	Controls n (%)	Crude OR (95% CI)	P-value
PPARG				
C _{rs1801282} C _{rs3856806}	847 (73.59)	1,403 (76.17)	1.00	
C _{rs1801282} T _{rs3856806}	267 (23.20)	338 (18.35)	1.31 (1.09–1.57)	0.004
G _{rs1801282} T _{rs3856806}	29 (2.52)	72 (3.91)	0.67 (0.43–1.04)	0.069
G _{rs1801282} C _{rs3856806}	8 (0.70)	29 (1.57)	0.46 (0.21–1.00)	0.046
PPARGC1B				
G _{rs7732671} G _{rs17572019}	1,070 (93.04)	1,737 (94.30)	1.00	
C _{rs7732671} A _{rs17572019}	79 (6.87)	103 (5.59)	1.25 (0.92–1.69)	0.155
PPARGC1A				
C _{rs2970847}	906 (78.78)	1,437 (78.01)	1.00	
T _{rs2970847}	244 (21.22)	405 (21.99)	0.96 (0.80–1.14)	0.619
PPARG, PPARGC1A, and PPARGC1B				
C _{rs1801282} C _{rs3856806} C _{rs2970847} G _{rs7732671} G _{rs17572019}	618 (53.79)	1,044 (56.71)	1.00	
C _{rs1801282} T _{rs3856806} C _{rs2970847} G _{rs7732671} G _{rs17572019}	198 (17.23)	259 (14.07)	1.29 (1.05–1.59)	0.017
C _{rs1801282} C _{rs3856806} T _{rs2970847} G _{rs7732671} G _{rs17572019}	159 (13.84)	277 (15.05)	0.97 (0.78–1.21)	0.783
C _{rs1801282} T _{rs3856806} T _{rs2970847} G _{rs7732671} G _{rs17572019}	59 (5.13)	64 (3.48)	1.56 (1.08–2.25)	0.017
C _{rs1801282} C _{rs3856806} C _{rs2970847} C _{rs7732671} A _{rs17572019}	56 (4.87)	58 (3.15)	1.63 (1.11–2.39)	0.011
G _{rs1801282} T _{rs3856806} C _{rs2970847} G _{rs7732671} G _{rs17572019}	21 (1.83)	42 (2.28)	0.84 (0.50–1.44)	0.534
C _{rs1801282} C _{rs3856806} T _{rs2970847} C _{rs7732671} A _{rs17572019}	12 (1.04)	23 (1.25)	0.88 (0.44–1.78)	0.725
G _{rs1801282} T _{rs3856806} T _{rs2970847} G _{rs7732671} G _{rs17572019}	7 (0.61)	26 (1.41)	0.45 (0.20–1.05)	0.060
Others	19 (1.65)	48 (2.61)	0.67 (0.39–1.15)	0.142

Note: Bold represents statistically significant values ($P < 0.05$).

Abbreviation: HCC, hepatocellular carcinoma.

HBV-infection-status subgroups. Results of haplotype analysis suggested that CTCGG, CTTGG, and CCCCA haplotypes of the order *PPARG* rs1801282 C>G and rs3856806 C>T, *PPARGC1A* rs2970847 C>T, *PPARGC1B* rs7732671 G>C, and *PPARGC1B* rs17572019 G>A polymorphisms might confer risk of HCC.

PPARG has been considered a HCC suppressor that contributes to the suppression of HCC-cell growth, angiogenesis, and migration.^{36–39} These primary results indicate that PPARG plays an important role in tumor suppression and may be a therapeutic target in HCC.³⁶ An SNP can lead to abnormal expression or to the generation of a defective form of the protein. Therefore, SNPs may be associated with the development of disease. *PPARG* rs1801282 C>G polymorphism is a missense SNP, which encodes a proline-to-alanine substitution.⁴⁰ Compared to the *PPARG* rs1801282 C allele, the *PPARG* rs1801282 G allele might influence the binding affinity to DNA elements and alter expression of PPARG-target genes and could then decrease transcriptional activation of the *PPARG* gene in vitro.^{8,41} It has been suggested that *PPARG* rs1801282 C→G substitution could improve insulin sensitivity and decrease body mass index (BMI) and susceptibility of T2DM.^{42,43} As such, it is believed that *PPARG* rs1801282 C>G polymorphism may decrease cancer susceptibility through insulin-related mechanisms. In the present case–control study, we found that *PPARG*

rs1801282 C>G polymorphism decreased the risk of HCC. Several meta-analyses found that this SNP decreased the susceptibility of colorectal cancer in Caucasians.^{44,45} Our findings were similar to those results. In future, more case–control studies are needed to confirm our findings and assess the interaction of genetic predisposition with environmental factors.

Rs3856806 C>T polymorphism, located in *PPARG* exon 6, is correlated with higher BMI.¹⁷ A C→T substitution is a synonymous SNP that encodes a histidine amino-acid residue in PPARG protein with either the rs3856806 C or T allele. *PPARG* rs3856806 C>T variants could influence energy metabolism and then presumably confer risk of T2DM.⁴⁶ The association between this SNP and the risk of cancer is unknown. Recently, some case–control studies found positive signals of *PPARG* rs3856806 C>T variants with the development of malignancy.^{21,47,48} The results of a meta-analysis suggested that *PPARG* rs3856806 C>T variants did not alter the susceptibility of cancer;⁴⁹ however, only four case–control studies with small samples were included in this pooled analysis. In this study, we found that *PPARG* rs3856806 C>T polymorphism was associated with an increased risk of HCC. It was proposed that synonymous SNPs may affect mRNA stability/structure, splicing accuracy, and codon usage.^{50,51} In combination with our findings, these results showed that *PPARG* rs3856806 C>T variants might be a risk

factor for HCC, probably through altering mRNA processing or translation and influencing the expression of *PPARG*. Therefore, in future, the function of *PPARG* rs3856806 C>T polymorphism needs to be explored further.

In this study, after Bonferroni correction, genotype distributions of *PPARG* rs1801282 C>G and rs3856806 C>T polymorphisms were still significantly different between HCC cases and controls, which indicated that our results were reliable. In addition, the results of power analysis also confirm the stability of our findings. We constructed seven haplotypes of *PPARG* rs1801282 C>G, *PPARG* rs3856806 C>T, *PPARGC1A* rs2970847 C>T, *PPARGC1B* rs7732671 G>C, and *PPARGC1B* rs17572019 G>A polymorphisms to evaluate the potential inherited patterns of haplotype. We found that CTCGG, CTTGG, and CCCCA haplotypes might increase the susceptibility to HCC. In addition, *PPARG* C_{rs1801282}T_{rs3856806} and G_{rs1801282}C_{rs3856806} haplotypes also influenced the risk of HCC. To the best of our knowledge, this study is the first investigation to explore the association of haplotypes in *PPARG* rs1801282 C>G, *PPARG* rs3856806 C>T, *PPARGC1A* rs2970847 C>T, *PPARGC1B* rs7732671 G>C, and *PPARGC1B* rs17572019 G>A polymorphisms with HCC susceptibility.

Just as with all epidemiological case–control studies, some limitations should be acknowledged. Firstly, this case–control study was hospital-based. All HCC cases and cancer-free controls were included from eastern China hospitals. Although the minor-allele frequency in controls was very close to data of Chinese populations (Table 2), the selection bias could not have been avoided. Secondly, we selected only five functional polymorphisms based on the publications, which could not represent an extensive view of these genetic predisposition in *PPARG*, *PPARGC1A*, and *PPARGC1B* genes. In future, a fine-mapping case–control study is needed to explore the potential relationships of *PPARG*, *PPARGC1A*, and *PPARGC1B* SNPs with HCC risk further. Thirdly, samples were moderate or small in some subgroups, and the power of the study might be limited in stratification analyses. Fourthly, for lack of sufficient samples, a replication study was not performed. Fifthly, as the distribution of *PPARG* rs3856806 C>T genotype frequencies did not accord with HWE in controls, our findings should be interpreted with much caution. Finally, due to lack of data for BMI, family history of HCC, other environmental factors, and lifestyle, these potential risk factors were not considered in our study. In future, large-sample studies with detailed individual data are needed to confirm our results.

In summary, to the best of our knowledge, this study is the first to explore the relationship of *PPARG*, *PPARGC1A*,

and *PPARGC1B* polymorphisms with HCC risk. Our findings suggest that *PPARG* polymorphisms may influence susceptibility to HCC. In addition, *PPARG*, *PPARGC1A*, and *PPARGC1B* haplotypes were associated with HCC risk.

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Disclosure

The authors report no conflicts of interest in this work.

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