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ORIGINAL RESEARCH

The relationship between *IGF2BP2* and *PPARG* polymorphisms and susceptibility to esophageal squamous-cell carcinomas in the eastern Chinese Han population

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Abstract: The aim of this case–control study was to assess whether *PPARG* and *IGF2BP2* polymorphisms confer susceptibility to esophageal squamous-cell carcinoma (ESCC). A total of 507 patients pathologically confirmed for ESCC and 1,496 age-, sex-, and residence-matched healthy individuals were enrolled. The *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms were selected and genotyped by SNPscan genotyping assays. Multivariable logistic analysis suggested that the *PPARG* rs3856806 C>T polymorphism might increase the risk of ESCC. In different stratified analyses, there were significant associations between *PPARG* rs3856806 C>T and risk of ESCC in female, never-smoking, drinking, and never-drinking subgroups. In addition, we also found that *PPARG* rs1801282 C>G increased ESCC risk in the never-smoking subgroup. There was significant difference in $C_{rs1470579}G_{rs4402960}C_{rs1801282}C_{rs3856806}$-haplotype distribution among ESCC cases and control subjects. In conclusion, our findings highlight that *PPARG* rs1801282 C>G and rs3856806 C>T polymorphisms are candidates for susceptibility to ESCC in the eastern Chinese Han population. The $C_{rs1470579}G_{rs4402960}C_{rs1801282}C_{rs3856806}$ haplotype is associated with susceptibility to ESCC.

Keywords: *PPARG*, *IGF2BP2*, polymorphism, risk, ESCC

Introduction

Esophageal cancer (EC) is a complex disease characterized by progressive dysphagia and emaciation. Because of aging and unhealthy lifestyles (eg, low intake of fruit and vegetables, the rising prevalence of smoking and drinking), EC constitutes a burden worldwide. Esophageal squamous-cell carcinoma (ESCC) is the most common subtype of EC in China.[1,2] The potential risk factors driving the high incidence of ESCC are not well understood. It is thought that poor nutritional status, insufficient fruit/vegetables intake, smoking, and drinking beverages at very high temperatures may be involved in the development of ESCC, though these potential risk factors cannot explain the total etiology of ESCC. Nowadays, it is considered that genetic variants may influence the risk of ESCC.

PPARs comprise a group of nuclear transcription factors, which are classified into three subtypes: PPARα, PPARβ, and PPARγ.[3] PPARγ is also named PPARG. In humans, the *PPARG* gene is located on chromosome 3p25. PPARG interacts with the retinoid X receptor, constructs a dipolymer, and then regulates its target

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genes, which are involved in cellular differentiation and metabolism of carbohydrates and lipids.[4] Polymorphisms in the *PPARG* gene are assumed to influence the development of malignancies and metabolism-related diseases. Pro12Ala (rs1801282 C>G) and His449His (rs3856806 C>T) polymorphisms are the two most common single-nucleotide polymorphism (SNPs) in the *PPARG* gene. Recently, a case–control study was conducted to assess the relationship of *PPARG* rs3856806 C>T with susceptibility to EC. The results indicated that *PPARG* rs3856806 C>T might be associated with the risk of EC.[5] In addition, the association between *PPARG* rs1801282 C>G polymorphism and EC risk was unknown.

IGF2BP2 binds to the 5′UTR of IGF2 mRNA and affects its translation.[6] Barghash et al reported that *IGF2BP2* expression correlated with poor survival in patients with esophageal adenocarcinoma and ESCC.[7] Case–control studies have indicated that *IGF2BP2* rs4402960 G>T might be associated with the risk of breast cancer[8] and colorectal cancer.[9] In addition, it has been reported that *IGF2BP2* rs1470579 A>C was associated with the risk of type 2 diabetes.[10,11] However, the association between *IGF2BP2* polymorphisms and EC risk was unclear.

The aim of this case–control study was to explore the potential relationship of genetic variations in *PPARG* and *IGF2BP2* with risk of ESCC in the eastern Chinese Han population. *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms were selected and genotyped by SNPscan genotyping assays in 507 patients with ESCC and 1,496 controls.

Materials and methods

Subjects

A total of 507 patients pathologically confirmed for ESCC from the Affiliated People's Hospital of Jiangsu University and the Affiliated Union Hospital of Fujian Medical University (mean age 62.77±8.01 years) were recruited in our study. The noncancer controls consisted of 1,496 age-, sex-, and residence-matched healthy individuals (mean age 62.77 ±8.84 years) without any cancer history or autoimmune diseases. All participants were enrolled between August 2013 and December 2016. EDTA-anticoagulated peripheral blood was collected after written consent had been signed. A questionnaire was used to obtain participants' risk factors and demographic variables. A body-mass index (BMI) ≥24 kg/m^2 was accepted as the criterion of obesity and overweight.[12,13] This study was approved by the institutional review boards of Jiangsu University (Zhenjiang, China) and Fujian Medical University (Fuzhou, China).

DNA extraction and genotyping

Genomic DNA was extracted from whole blood using a DNA kit (Promega, Madison, WI, USA). *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T genotypes were determined by double ligation and multiplex-fluorescence polymerase chain reaction (SNPscan; Genesky Biotechnologies, Shanghai, China).[14] For quality control, 80 samples (4%) were randomly selected from the 2,003 DNA samples and genotyped again by another technician. Genotypes of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms were confirmed.

Statistical analysis

Continuous variables (age, BMI, height, and weight) are expressed as means ± SD. Comparisons of these continuous variables between two groups were performed using Student's *t*-test. The χ^2 test was used to compare categorical variables (*PPARG* and *IGF2BP2* genotypes, BMI, sex, age, and smoking status and alcohol use). We checked the deviations for Hardy–Weinberg equilibrium in normal controls with an Internet-based calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl).[15–21] Statistical significance was defined as $P<0.05$ (two-tailed). The relationships of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms with ESCC susceptibility were determined by crude odds ratios (ORs) and 95% CIs. Adjusted for BMI, age, sex, alcohol use, and smoking status, multivariate linear regression was used to assess the potential association further among these polymorphisms and susceptibility to ESCC. SAS 9.4 software for Windows (SAS Institute, Cary, NC, USA) was used to analyze the data. SHEsis software (http://analysis.bio-x.cn/myanalysis.php; Bio-X, Shanghai, China) was used online to construct the haplotypes.[22–24]

Results

Baseline characteristics

Characteristics of 507 ESCC cases and 1,496 controls included in this case–control study are presented in Table 1. ESCC cases and controls were well matched on age and sex, as shown by χ^2 tests (P=0.994 and P=0.406, respectively). As shown in Table 1, significant differences were found on smoking status and alcohol use between cases and controls ($P<0.001$). The primary information for *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T SNPs is shown in Table 2. For these four genotyped SNPs, the successful ratio was 99.45%–99.5% in all 2,003 DNA samples. The concordance rates of

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

	Cases (n=507)		Controls (n=1,496)		*P*-value[a]
	n	%	n	%	
Age (years), mean ± SD	62.77±8.01		62.77±8.84		0.994
Age (years)					0.225
<63	271	53.45	753	50.33	
≥63	236	46.55	743	49.67	
Sex					0.406
Male	377	74.36	1,084	72.46	
Female	130	25.64	412	27.54	
Tobacco use					<0.001
Never	247	48.72	1,090	72.86	
Ever	260	51.28	406	27.14	
Alcohol use					<0.001
Never	341	67.26	1,329	88.84	
Ever	166	32.74	167	11.16	
Height (cm)	166±7.29		166.1±7.08		0.743
Weight (kg)	61.54±9.83		66.11±9.92		<0.001
BMI (kg/m^2), mean ± SD	22.27±2.90		23.91±3.03		<0.001
BMI (kg/m^2)					<0.001
<24	370		779		
≥24	137		717		

Note: [a]Two-sided χ^2 test and Student's *t*-test.
Abbreviations: ESCC, esophageal squamous-cell carcinoma; BMI, body-mass index.

quality-control testing were 100%. Minor allele frequency of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T SNPs in controls was close to the minor allele-frequency data for Chinese (Table 2). In controls, the genotype frequencies for *PPARG* rs1801282 C>G and rs3856806 C>T polymorphisms were in Hardy–Weinberg equilibrium (Table 2).

Association of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms with ESCC risk

The genotypes of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms are summarized in Table 3. In single-locus analyses, the genotype frequencies of *PPARG* rs3856806 C>T were 54.56% (CC), 39.09% (CT), and 6.35% (TT) in ESCC patients and 59.7% (CC), 36.13% (CT), and 4.16% (TT) in controls. When the *PPARG* rs3856806 CC homozygote genotype was used as the reference group, the *PPARG* rs3856806 CT genotype was correlated with a significantly increased risk of ESCC (CT vs CC, adjusted OR 1.28, 95% CI=1.02–1.6; *P*=0.033). When the *PPARG* rs3856806 CC homozygote genotype was used as the reference group, the *PPARG* rs3856806 TT genotype was correlated with a borderline significantly increased risk of ESCC (TT vs CC, adjusted OR 1.55, 95% CI=0.96–2.50; *P*=0.074). In the recessive model, when the *PPARG* rs3856806 CC/CT genotypes were used as the reference group, the *PPARG* rs3856806 TT homozygote genotype was not associated with susceptibility for ESCC (adjusted OR 1.41, 95% CI=0.88–2.26; *P*=0.153). In the dominant model, *PPARG* rs3856806 CT/TT genotypes were associated with an increased risk of ESCC compared with the *PPARG* rs3856806 CC genotype (adjusted OR 1.31, 95% CI=1.06–1.63; *P*=0.014) (Table 3). Logistic regression analyses showed that *PPARG* rs1801282 C>G and *IGF2BP2* rs1470579 A>C, rs4402960 G>T polymorphisms were not correlated with the susceptibility for ESCC (Table 3).

Association of *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms with ESCC risk in different stratification groups

To determine the potential effects of *PPARG* rs1801282 C>G genotypes on ESCC risk in different subgroups according to BMI, age, sex, and smoking and drinking status, we carried out stratified analyses (Table 4). In the never-smoking subgroup, after adjustment for sex, age, BMI, and alcohol use, we found that the *PPARG* rs1801282 C>G polymorphism increased ESCC risk in two genetic models (CG vs CC,

Table 2 Primary information for *PPARG* rs1801282 C>G, rs3856806 C>T, and *IGF2BP2* 1470579 A>C, rs4402960 G>T polymorphisms

Genotyped SNPs	Chromosome	Chromosome position (NCBI build 38)	MAF for Chinese in database	MAF in our controls (n=1,496)	*P*-value for HWE test in our controls	Genotyping method	Genotyping value (%)
PPARG rs1801282 C>G	3	12351626	0.07	0.05	0.911	SNPscan	99.5
PPARG rs3856806 C>T	3	12434058	0.25	0.22	0.083	SNPscan	99.5
IGF2BP2 rs1470579 A>C	3	185811292	0.27	0.25	0.002	SNPscan	99.5
IGF2BP2 rs4402960 G>T	3	185793899	0.26	0.25	0.002	SNPscan	99.45

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

Table 3 Logistic regression analyses of association between *PPARG* rs1801282 C>G, rs3856806 C>T and *IGF2BP2* 1470579 A>C, rs4402960 G>T polymorphisms and risk of ESCC

Genotype	ESCC cases (n=507)		Controls (n=1,496)		Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
	n	%	n	%				
PPARG rs1801282 C>G								
CC	440	87.3	1,334	89.59	1			
GC	63	12.5	151	10.14	1.26 (0.92–1.73)	0.144	1.24 (0.88–1.73)	0.219
GG	1	0.20	4	0.27	0.76 (0.08–6.79)	0.804	1.08 (0.11–10.5)	0.950
GC+GG	64	12.7	155	10.41	1.25 (0.92–1.71)	0.156	1.23 (0.88–1.72)	0.217
CC+GC	503	99.8	1,485	99.73	1		1	
GG	1	0.20	4	0.27	0.74 (0.08–6.62)	0.786	1.05 (0.11–10.26)	0.966
G allele	65	6.45	159	5.34				
PPARG rs3856806 C>T								
CC	275	54.56	889	59.7	1			
CT	197	39.09	538	36.13	1.18 (0.96–1.46)	0.125	1.28 (1.02–1.6)	0.033
TT	32	6.35	62	4.16	1.66 (1.06–2.6)	0.026	1.55 (0.96–2.5)	0.074
CT+TT	229	45.44	600	40.30	1.23 (1.01–1.51)	0.043	1.31 (1.06–1.63)	0.014
CC+CT	472	93.65	1,427	95.84	1		1	
TT	32	6.35	62	4.16	1.56 (1.01–2.42)	0.047	1.41 (0.88–2.26)	0.153
T allele	261	25.89	662	22.23				
IGF2BP2 1470579 A>C								
AA	280	55.56	855	57.42	1		1	
AC	194	38.49	517	34.72	1.14 (0.92–1.41)	0.218	1.09 (0.87–1.37)	0.453
CC	30	5.95	117	7.86	0.78 (0.51–1.19)	0.252	0.78 (0.5–1.22)	0.282
AC+CC	224	44.44	634	42.58	1.08 (0.88–1.32)	0.465	1.04 (0.83–1.29)	0.748
AA+AC	474	94.05	1,372	92.14	1		1	
CC	30	5.95	117	7.86	0.74 (0.49–1.12)	0.159	0.76 (0.49–1.17)	0.213
C allele	254	25.20	751	25.22				
IGF2BP2 rs4402960 G>T								
GG	294	58.45	872	58.56	1		1	
GT	179	35.59	506	33.98	1.04 (0.84–1.29)	0.698	0.99 (0.78–1.24)	0.904
TT	30	5.96	111	7.45	0.8 (0.52–1.22)	0.295	0.83 (0.53–1.29)	0.402
GT+TT	209	41.55	617	41.44	1.01 (0.82–1.23)	0.694	0.96 (0.77–1.2)	0.737
GG+GT	473	94.04	1,378	92.55	1		1	
TT	30	5.96	111	7.45	0.79 (0.52–1.19)	0.261	0.84 (0.54–1.29)	0.418
T allele	239	23.76	728	24.45				

Note: [a]Adjusted for age, sex, BMI, alcohol use, and smoking status.
Abbreviations: ESCC, esophageal squamous-cell carcinoma; BMI, body-mass index; OR, odds ratio.

adjusted OR 1.54, 95% CI 1.01–2.35, *P*=0.047; CG/GG vs CC, adjusted OR 1.54, 95% CI 1.01–2.34, *P*=0.044 [Table 4]).

Table 5 shows genotype frequencies of *PPARG* rs3856806 C>T in different subgroups. Significantly increased susceptibility to ESCC associated with the *PPARG* rs3856806 C>T polymorphism was found among several subgroups (Table 5). In the female subgroup after adjustment for BMI, age, and smoking and drinking status, the *PPARG* rs3856806 CT/TT genotypes were associated with increased ESCC risk compared with the *PPARG* rs3856806 CC genotype (CT/TT vs CC, adjusted OR 1.55, 95% CI 1.02–2.35; *P*=0.041 [Table 5]). In the never-smoking subgroup after adjustment for BMI, age, sex, and drinking status, we found that *PPARG* rs3856806 CT/TT genotypes increased ESCC risk compared with the *PPARG* rs3856806 CC genotype (CT/TT vs CC, adjusted OR 1.37, 95% CI 1.03–1.82; *P*=0.032 [Table 5]). In the drinking subgroup after adjustment for BMI, age, sex, and smoking status, significantly increased risk of ESCC associated with the *PPARG* rs3856806 C>T polymorphism was also found (TT vs CC, adjusted OR 3.36, 95% CI 1.05–12.74, *P*=0.041; TT vs CT/CC, adjusted OR 3.58, 95% CI 1.04–12.29, *P*=0.043 [Table 5]). In the never-drinking subgroup after adjustment for BMI, age, sex, and smoking status, significantly increased risk of ESCC associated with the *PPARG* rs3856806 C>T polymorphism was also found (CT vs CC, adjusted OR 1.37, 95% CI 1.06–1.77, *P*=0.015; CT/TT vs CC, adjusted OR 1.37, 95% CI 1.07–1.75, *P*=0.013

Table 4 Stratified analyses between *PPARG* rs1801282 C>G polymorphism and ESCC risk by sex, age, BMI, smoking status, and alcohol consumption

	***PPARG* rs1801282 C>G (case/control)[a]**			**Adjusted OR[b] (95% CI); *P*-value**				
	CC	**CG**	**GG**	**CC**	**CG**	**GG**	**CG/GG**	**GG vs (CG/CC)**
Sex								
Male	328/963	47/112	0/3	1	1.21 (0.81–1.79); *P*=0.351	–	1.18 (0.8–1.75); *P*=0.407	–
Female	112/371	16/39	1/1	1	1.55 (0.81–2.99); *P*=0.188	3.96 (0.25–63.97); *P*=0.332	1.62 (0.86–3.08); *P*=0.138	3.77 (0.23–60.91); *P*=0.349
Age, years								
<63	207/679	28/66	1/2	1	1.43 (0.85–2.41); *P*=0.179	1.78 (0.13–24.51); *P*=0.665	1.43 (0.86–2.39); *P*=0.172	1.71 (0.13–23.44); *P*=0.687
≥63	233/655	35/85	0/2	1	1.14 (0.73–1.78); *P*=0.555	–	1.14 (0.73–1.77); *P*=0.571	–
Smoking status								
Never	210/976	34/106	1/4	1	1.54 (1.01–2.35); *P*=0.047	1.34 (0.14–12.59); *P*=0.796	1.54 (1.01–2.34); *P*=0.044	1.28 (014–11.97); *P*=0.830
Ever	230/358	29/45	0/0	1	0.92 (0.54–1.57); *P*=0.757	–	0.92 (0.54–1.56); *P*=0.746	–
Alcohol consumption								
Never	296/1,186	41/134	1/3	1	1.20 (0.82–1.76); *P*=0.348	1.82 (0.18–18.63); *P*=0.614	1.22 (0.84–1.78); *P*=0.305	1.78 (0.17–18.25); *P*=0.626
Ever	144/148	22/17	0/1	1	1.41 (0.67–3); *P*=0.369	–	1.32 (0.63–2.77); *P*=0.457	–
BMI (kg/m^2)								
<24	319/695	47/78	1/1	1	1.32 (0.87–1.99); *P*=0.193	2.3 (0.14–37.56); *P*=0.558	1.34 (0.89–2.02); *P*=0.165	2.23 (0.14–36.38); *P*=0.574
≥24	121/639	16/73	0/3	1	1.13 (0.63–2.03); *P*=0.691	–	1.09 (0.61–1.96); *P*=0.775	–

Notes: [a]For *PPARG* rs1801282 C>G, genotyping was successful in 507 (99.41%) ESCC cases and 1,496 (99.53%) controls; [b]adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Abbreviations: ESCC, esophageal squamous-cell carcinoma; BMI, body-mass index; OR, odds ratio.

[Table 5]). In addition, there was no significant risk of ESCC correlated with the *IGF2BP2* rs1470579 A>C and rs4402960 G>T polymorphisms evident among any subgroup (data not shown).

SNP haplotypes

Using the SHEsis software,[22] we constructed eight haplotypes (Table 6). There were significant differences in the CGCC haplotype of the order rs1470579 A>C, rs4402960 G>T, rs1801282 C>G and rs3856806 C>T polymorphism distribution among ESCC cases and the control subjects (OR 2.23, 95% CI=1.09–4.59; *P*=0.025 [Table 6]).

Discussion

In this case–control study, we explored the associations between the *PPARG* rs1801282 C>G and rs3856806 C>T and *IGF2BP2* rs1470579 A>C and rs4402960 G>T SNPs and risk of ESCC in the eastern Chinese Han population. Multivariable logistic analysis suggested that *PPARG* rs3856806 C>T might be associated with an increased risk of ESCC. In different stratified analyses, there were significant associations between this polymorphism and risk of ESCC in the female, never-smoking, drinking, and never-drinking subgroups. In addition, we also found that *PPARG* rs1801282 C>G increased ESCC risk in the never-smoking subgroup. To the best of our knowledge, this is the first study to identify a potential association between *PPARG* rs1801282 C>G and rs3856806 C>T polymorphisms and increased risk of ESCC in Asians.

PPARG is a member of the nuclear hormone-receptor superfamily and may possess anti-inflammatory properties.[25] PPARG also plays an important role in cell proliferation/differentiation, which affects the development and progression of cancer.[26,27] The *PPARG* rs1801282 C>G polymorphism is located in the exon B region of the *PPARG* gene. Deeb et al reported that this SNP was associated with decreased transactivation activity and lower BMI and promoted insulin sensitivity.[28] A recent meta-analysis suggested that *PPARG* rs1801282 C>G polymorphism is a candidate for susceptibility to Asians.[29] The association

Table 5 Stratified analyses between *PPARG* rs3856806 C>T polymorphism and ESCC risk by sex, age, BMI, smoking status, and alcohol consumption

	PPARG rs3856806 C>T (case/control)[a]			Adjusted OR[b] (95% CI); *P*-value				
	CC	CT	TT	CC	CT	TT	CT/TT	TT vs (CT/CC)
Sex								
Male	206/632	144/403	25/43	1	1.22 (0.93–1.59); *P*=0.146	1.57 (0.89–2.77); *P*=0.116	1.26 (0.98–1.63); *P*=0.078	1.46 (0.84–2.54); *P*=0.185
Female	69/257	53/135	7/19	1	1.53 (0.99–2.36); *P*=0.054	1.57 (0.61–4.03); *P*=0.351	1.55 (1.02–2.35); *P*=0.041	1.33 (0.53–3.37); *P*=0.543
Age, years								
<63	131/457	89/259	16/31	1	1.35 (0.96–1.9); *P*=0.081	1.6 (0.78–3.28); *P*=0.199	1.37 (0.99–1.9); *P*=0.061	1.42 (0.7–2.87); *P*=0.331
≥63	144/432	108/279	16/31	1	1.26 (0.93–1.72); *P*=0.136	1.53 (0.79–2.96); *P*=0.209	1.31 (0.98–1.77); *P*=0.073	1.4 (0.73–2.68); *P*=0.306
Smoking status								
Never	129/645	103/396	13/45	1	1.35 (1.01–1.82); *P*=0.044	1.35 (0.7–2.6); *P*=0.37	1.37 (1.03–1.82); *P*=0.032	1.2 (0.63–2.29); *P*=0.578
Ever	146/244	94/142	19/17	1	1.21 (0.84–1.73); *P*=0.302	1.82 (0.86–3.84); *P*=0.117	1.27 (0.9–1.79); *P*=0.171	1.69 (0.81–3.52); *P*=0.162
Alcohol consumption								
Never	179/793	142/472	17/58	1	1.37 (1.06–1.77); *P*=0.015	1.24 (0.7–2.21); *P*=0.458	1.37 (1.07–1.75); *P*=0.013	1.10 (0.63–1.94); *P*=0.740
Ever	96/96	55/66	15/4	1	1.03 (0.62–1.72); *P*=0.901	3.66 (1.05–12.74); *P*=0.041	1.19 (0.73–1.94); *P*=0.48	3.58 (1.04–12.29); *P*=0.043
BMI (kg/m^2)								
<24	207/469	135/268	25/37	1	1.23 (0.93–1.62); *P*=0.156	1.53 (0.86–2.72); *P*=0.146	1.27 (0.97–1.67); *P*=0.08	1.42 (0.81–2.51); *P*=0.222
≥24	68/420	62/270	7/25	1	1.41 (0.96–2.07); *P*=0.080	1.66 (0.68–4.05); *P*=0.268	1.43 (0.98–2.07); *P*=0.063	1.43 (0.6–3.44); *P*=0.423

Notes: [a]For *PPARG* rs3856806 C>T, genotyping was successful in 507 (99.41%) ESCC cases and 1,496 (99.53%) controls; [b]adjusted for multiple comparisons (age, sex, BMI, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model.
Abbreviations: ESCC, esophageal squamous-cell carcinoma; BMI, body-mass index; OR, odds ratio.

between *PPARG* rs1801282 C>G and risk of ESCC has not been studied before. In this study, we found that the *PPARG* rs1801282 CG genotype was more frequent in ESCC patients in the never-smoking subgroup, which was in accordance with the results of the meta-analysis just mentioned. The function of the *PPARG* rs1801282 C>G SNP remains to be investigated in ESCC patients.

Table 6 Haplotype frequencies (%) in cases and controls and risk of ESCC

	Cases (n=1,006)		Controls (n=2,978)		Crude OR (95% CI)	*P*-value
	n	%	n	%		
AGCC	543	53.98	1,679	56.38	Reference	
CTCC	174	17.30	565	18.97	0.95 (0.78–1.16)	0.624
AGCT	164	16.30	430	14.44	1.18 (0.96–1.45)	0.113
CTCT	45	4.47	107	3.59	1.3 (0.91–1.87)	0.153
AGGT	36	3.68	79	2.65	1.41 (0.94–2.12)	0.096
CTGT	13	1.29	34	1.14	1.18 (0.62–2.26)	0.611
CGCC	13	1.29	18	0.60	2.23 (1.09–4.59)	0.025
AGGC	9	0.89	30	1.01	0.93 (0.44–1.97)	0.845
Others	9	0.89	36	1.21	0.77 (0.37–1.62)	0.492

Note: With order of rs1470579 A>C, rs4402960 G>T, rs1801282 C>G and rs3856806 C>T in gene position.
Abbreviations: ESCC, esophageal squamous-cell carcinoma; OR, odds ratio.

There was a difference in genotype distribution of the *PPARG* rs3856806 C>T polymorphism between ESCC patients and controls. The *PPARG* rs3856806 CT and TT/CT genotypes were more frequent in ESCC patients compared with healthy controls, suggesting that the *PPARG* rs3856806 TT/CT and CT genotypes might contribute to the development of ESCC. The *PPARG* rs3856806 C>T polymorphism is located in the exon of the *PPARG* gene. It is difficult to illustrate the exact function of a synonymous SNP. It is proposed that *PPARG* rs3856806 C→T substitution may disrupt the splice site,[30] and then affect the expression of PPARG. A meta-analysis suggested that *PPARG* rs3856806 C>T is marginally associated with cancer susceptibility,[31] and our results were similar.

In the present investigation, we constructed eight haplotypes to study inherited patterns. We found that the $C_{rs1470579}G_{rs4402960}C_{rs1801282}C_{rs3856806}$ haplotype was associated

with susceptibility for ESCC. Comparing the CGCC with the AGCC haplotype in the order of rs1470579 A>C, rs4402960 G>T, rs1801282 C>G, and rs3856806 C>T polymorphisms, we found that A→C variation in the rs1470579 A>C locus led to susceptibility of the haplotype to ESCC. Several case–control studies have reported that *IGF2BP2* rs1470579 A>C was associated with type 2 diabetes mellitus.[11,32–34] However, a potential association between *IGF2BP2* rs1470579 A>C polymorphism and ESCC risk was not found in our case–control study. In the future, more case–control studies with large samples and detailed risk factors should be carried out to confirm or refute our findings.

There were some limitations in our study. Firstly, this case–control study was limited by the moderate sample size of ESCC patients, which might lead to suboptimal power to identify true associations in the stratified analyses. Secondly, the controls were recruited from two local hospitals, and might not represent the general Chinese population well; this possible bias should not be ignored. Thirdly, only some functional SNPs in the *PPARG* and *IGF2BP2* genes were selected. The relationship of *PPARG* and *IGF2BP2* variants was not fully explored. In the future, a fine-mapping study should be conducted. Fourthly, detailed information on metastasis and survival of ESCC was not available at the time of research, which restricted further analysis on the potential role of *PPARG* and *IGF2BP2* variants in ESCC progression and prognosis. Finally, for lack of some environmental risk factors, such as lifestyle and intake of fruit/vegetables, the interaction of gene variants with environmental risk factors was not considered.

Conclusion

Our findings highlight that *PPARG* rs1801282 C>G and rs3856806 C>T polymorphisms are candidates for susceptibility to ESCC in the eastern Chinese Han population. A fine-mapping study is required to confirm these preliminary findings.

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Disclosure

The authors report no conflicts of interest in this work.

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