IL18 rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms and risk of gastric cardiac adenocarcinoma

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Abstract. The present study was conducted to investigate the association between gastric cardiac adenocarcinoma (GCA) and four functional single-nucleotide polymorphisms (SNPs), including interleukin 18 (*IL18*) rs360719 A>G, IL18 receptor 1 *(IL18R1)* rs13015714 G>T, IL18 receptor accessory protein *(IL18RAP)* rs917997 C>T and interleukin 28B (*IL28B)* rs8099917 T>G variants. A hospital-based case-control study was performed to evaluate the genetic effects of these SNPs. A total of 243 GCA cases and 476 controls were enrolled in this study. A custom-by-design 48-Plex SNPscan™ kit was used to determine the genotypes. When the *IL18* rs360719 AA homozygote genotype was used as the reference group, the AG genotype was not associated with the risk for GCA; the GG genotype was also not associated with the risk for GCA. In the dominant model, the *IL18* rs360719 AG/GG variants were not associated with the risk for GCA, compared with the *IL18* rs360719 AA genotype. In the recessive model, when the *IL18R1* rs13015714 AA/AG genotypes were used as the reference group, the GG homozygote genotype was not associated with risk for GCA. No association was observed between *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms and the risk for GCA. These results demonstrated that the functional polymorphisms *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G do not contribute to GCA susceptibility. However, as the statistical power of our study was limited, large well-designed studies and further functional investigations are required to confirm our findings.

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Abbreviations: CI, confidence interval; GCA, gastric cardiac adenocarcinoma; IL18, interleukin 18; OR, odds ratio; SNP, single-nucleotide polymorphism

Key words: interleukin 18, polymorphisms, gastric cardiac adenocarcinoma, molecular epidemiology

Introduction

Gastric cardiac adenocarcinoma (GCA) is one of the most common malignant tumors and among the leading causes of cancer-related mortality worldwide. Genetic as well as environmental factors may be included in the etiology of GCA (1). Single-nucleotide polymorphisms (SNPs), which account for >90% of genetic variations, may affect gene function (2). Individual differences in disease susceptibility have been suggested to be affected by SNPs (3).

Interleukin 18 (IL18), initially described as an interferon (IFN)-γ-inducing factor, may upregulate several cytokines, including IFN-γ, tumor necrosis factor-α and IL1β (4). IL18 participates in innate as well as acquired immunity and is largely produced by activated macrophages, Kupffer cells and dendritic cells (5,6). IL18 also promotes T helper cell type 1 (Th1) differentiation. The major functions of IL18 include production of IFN-γ by activated T lymphocytes and natural killer (NK) cells (5), and enhancement of T- and NK-cell maturation (7). IL18 may also induce proinflammatory cytokines and chemokines (8,9) and augment Fas ligand-mediated and perforin-dependent cytotoxicity of T and NK cells (10-12). Furthermore, IL18-deficient mice exhibited a reduction in IFN-γ production, NK-cell activity impairement and defective Th1 response (13).

As one of the main products of inflammasomes, IL18 exerts profound effects on carcinogenesis and tumor progression (14). The IL18 receptor comprises the IL18 receptor

accessory protein (IL18RAP) and IL18 receptor 1 (IL18R1) protein (15,16).

Upon binding to its receptor IL18R1 protein, IL18 triggers the recruitment of IL18RAP and initiates signalling. As regards preventing colon adenocarcinoma development, IL18 plays a role in MyD88-mediated signalling (17). IL18RAP has been shown to be crucial for IL18 signalling, forms the signalling chain of this receptor complex and results in the production of IFN-γ (18). The two subunits of the IL18 receptor are mainly expressed on Th1 cells in response to interferon-α and/or IL12 (19). IL18RAP was also recently found to be associated with inflammatory bowel disease (20). The *IL18R1* and *IL18RAP* genes have been found to be associated with atherosclerosis and its cardiovascular complications (21).

IL18 rs360719 polymorphism leads to loss of the octamer (OCT)-1 transcription factor binding site. OCT-1 is known to be a ubiquitously expressed factor and is involved in the regulation of several genes; it may also repress the expression of certain cytokines (22). Allele A of rs917997, a SNP 1.5 kb downstream of *IL18RAP*, was found to be strongly associated with coeliac disease susceptibility (23). This allele is also correlated with lower mRNA levels in whole blood. Furthermore, the *IL18RAP* GA haplotype of rs13015714 and rs917997 exhibited the strongest association with coeliac disease (23). Recently, genome-wide association studies have identified *IL18RAP* SNP rs917997, located on chromosome 2, as protective against type 1 diabetes (T1D) (24). The SNP, a C-to-T substitution in the 3'-untranslated region of *IL18RAP*, has been associated with decreased gene expression in the peripheral blood (25).

Interleukin 28B (*IL28B*) rs8099917 T>G polymorphism has been found to be associated with the response to IFN-γ-based antiviral therapy during the natural course of hepatitis C virus infection and following liver transplantation (26,27).

The IL18 receptor comprises IL18RAP and IL18R1. IL18RAP has been shown to be crucial for IL18 signalling, resulting in the production of IFN-γ. Allele A of *IL18RAP* rs917997 was found to be strongly associated with coeliac disease susceptibility (23). This allele also exerted a significant allele dosage effect on IL18RAP mRNA expression in whole blood. The *IL18RAP* rs917997 C allele is strongly associated with a protective effect in Barrett's esophagus and esophageal adenocarcinoma, and the CC genotype at *IL18RAP* locus rs917997 was associated with a protective effect against esophageal disease, which is in accordance with our results in stratification analyses (28).

In this study, we hypothesized that these SNPs may alter the individual risk of GCA. Thus, genotyping analyses for the four SNPs were performed in a Chinese Han population of 243 GCA cases and 476 control subjects.

Patients and methods

Ethics approval of the study protocol. This study was approved by the Institutional Review Board of Jiangsu University (Zhenjiang, China). All the subjects included in the study provided written informed consent and the study protocol complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Table I. Distribution of selected demographic variables and risk factors in GCA cases and controls.

Variables	Cases, n (%) (n=243)	Controls (n=476)	P-value[a]
Age (years)			0.923
<65	126 (51.9)	245 (51.5)	
≥65	117 (48.1)	231 (48.5)	
Mean ± SD	64.90±8.65	64.76±7.46	0.832
Sex			0.197
Male	159 (65.4)	288 (60.5)	
Female	84 (34.6)	188 (39.5)	
Tobacco use			**0.004**
Never	144 (59.3)	333 (70.0)	
Ever	99 (40.7)	143 (30.0)	
Alcohol use			0.217
Never	167 (68.7)	348 (73.1)	
Ever	76 (31.3)	128 (26.9)	
LN metastasis			
Present	122 (55.5)		
Absent	98 (44.5)		
TNM stage			
I	24 (12.2)		
II	34 (17.3)		
III	101 (51.6)		
IV	37 (18.9)		

[a]Two-sided χ^2 test and Student's t-test. Bold print denotes statistical significance (P<0.05). LN, lymph node (LN information was available in 220 GCA cases); TNM, tumor-node-metastasis (TNM stage information was available in 196 GCA cases); GCA, gastric cardiac adenocarcinoma; SD, standard deviation.

Study subjects. The 243 GCA patients included in the case group were consecutively recruited at the Affiliated People's Hospital of Jiangsu University and the Affiliated Hospital of Jiangsu University (Zhenjiang, China) between October, 2008 and July, 2010. In all the cases, a definite diagnosis was based on pathological examination. Tumor-node-metastasis (TNM) stage was defined according to the 7th edition of the Union for International Cancer Control TNM staging guidelines (29). The exclusion criteria included patients who previously had any primary or metastatic cancer and received radiotherapy or chemotherapy. In this study, 476 cancer-free controls were also included during the same time period, of whom 380 controls were recruited from the two aforementioned hospitals and were matched to the cases for age (±5 years) and sex; another 96 controls were recruited from hospitals in the city of Changzhou (which is adjacent to Zhenjiang) (30). The majority of the controls were admitted to the hospitals to receive treatment for trauma.

Each patient was personally questioned by a trained investigator to obtain information on demographic data (e.g., age and sex) and related environmental risk factors (including tobacco use and alcohol consumption), using a pre-tested questionnaire. A 2-ml venous blood sample was collected from each subject

Table II. Primary information for *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms.

Genotyped SNPs	*IL18* rs360719 A>G	*IL18R1* rs13015714 G>T	*IL18RAP* rs917997 C>T	*IL28B* rs8099917 T>G
Chromosome	11	2	2	19
Location	5' flanking	5' flanking	3' flanking	5' flanking
Chr Pos (Genome Build 36.3)	111541359	102338297	102437000	44435005
Regulome database score[a]	2b	6	No data	4
TFBS[b]	Y	-	-	-
MAF for Chinese in database	0.142	0.547	0.488	0.035
MAF in our controls (n=476)	0.125	0.512	0.495	0.048
P-value for HWE test in our controls	0.591	0.466	0.814	0.273
Genotyping value (%)	97.08	97.50	96.94	97.50

[a]http://www.regulomedb.org/. [b]http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm. IL18 rs360719 A>G MAF information was available for Japanese subjects in Tokyo and Han Chinese subjects in Beijing. TFBS, transcription factor-binding site; *IL18*, interleukin 18; *IL18R1*, IL18 receptor 1; *IL18RAP*, IL18 receptor accessory protein; *IL28B*, interleukin 28B; SNP, single-nucleotide polymorphism; Chr Pos, chromosome position; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

after the investigation. Individuals who smoked one cigarette per day for >1 year were classed as smokers, whereas subjects who consumed ≥3 alcoholic drinks per week for >6 months were defined as alcohol drinkers.

DNA extraction and genotyping analysis. Blood samples were collected from the subjects using vacutainers and drawn into tubes lined with EDTA. The QIAamp DNA Blood Mini kit (Qiagen, Berlin, Germany) was used to extract genomic DNA from peripheral blood (31). Sample DNA (10 ng) was amplified by polymerase chain reaction (PCR) according to the manufacturer's recommendations. As previously described, a custom-by-design 48-Plex SNPscan™ kit (Genesky Biotechnologies, Inc., Shanghai, China) was used to determine the genotypes of the four SNPs (32-35). This kit was developed according to patented SNP genotyping technology by Genesky Biotechnologies, which was mainly based on double ligation and multiplex fluorescence PCR. To guarantee genotyping quality, repeated analyses were accomplished by randomly selecting 4% of samples with high DNA quality.

Statistical analyses. Differences in the distribution of demographic characteristics, selected variables and genotypes of the *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G variants between the cases and controls were estimated using the χ^2 test. The associations between the four SNPs and susceptibility to GCA were evaluated by calculating the odds ratios (ORs) and their 95% confidence intervals (CIs) using logistic regression analyses for crude and adjusted ORs after adjusting for age, sex, smoking and drinking status. The Hardy-Weinberg equilibrium (HWE) was tested by a goodness-of-fit χ^2 test to compare the observed genotype frequencies to those expected among the control group. All the statistical analyses were performed with SAS 9.1.3 software (SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of the study population. The characteristics of the cases and controls included in this study are summarized in Table I. The cases and controls appeared to be adequately matched for age and sex, as suggested by the χ^2 tests (P=0.923 and P=0.197, respectively). As shown in Table I, no significant difference in drinking status was observed between the cases and the controls (P=0.217), but the smoking rate was higher in GCA patients compared with that in control subjects (P=0.004). Lymph node metastasis information was available in 220 (90.5%) of the 243 GCA patients and regional lymph node metastasis was present in 122 (55.5%) cases. TNM stage data were available in 196 (80.7%) of the 243 patients (stage I, 24; stage II, 34; stage III, 101; and stage IV, 37 patients) (Table I). The primary information for the four genotyped SNPs is presented in Table II. For the four SNPs, genotyping was successful, ranging from 96.94 to 97.50% in the 719 samples. The concordance rates of repeated analyses were 100%. Minor allele frequency (MAF) in our controls was similar to the MAF for Chinese subjects in the database for all four SNPs (Table II). The observed genotype frequencies for these four polymorphisms in the controls were all in HWE (Table II).

Associations between IL18 rs360719 A>G, IL18R1 rs13015714 G>T, IL18RAP rs917997 C>T and IL28B rs8099917 T>G polymorphisms and risk of GCA. The genotype distributions of *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G in the cases and the controls are presented in Table III. In the single locus analyses, the genotype frequencies of *IL18* rs360719 A>G were 74.47% (AA), 24.26% (AG) and 1.28% (GG) in the cases and 76.24% (AA), 22.46% (AG) and 1.30% (GG) in the control subjects; the differences were not statistically significant (P=0.868). When the *IL18* rs360719 AA homozygote genotype was used as the reference group, the AG genotype was not associated with the risk for GCA (AG vs. AA: adjusted OR=1.08,

Table III. Logistic regression analyses of associations between *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms and risk of GCA.

Genotype	Cases, n (%) (n=243)	Controls, n (%) (n=476)	Crude OR (95% CI)	P-value	Adjusted OR[a] (95% CI)	P-value
IL18 rs360719 A>G						
AA	175 (74.47)	353 (76.24)	1.00	1.00		
AG	57 (24.26)	104 (22.46)	1.11 (0.76-1.60)	0.595	1.08 (0.75-1.57)	0.679
GG	3 (1.28)	6 (1.30)	1.01 (0.25-4.08)	0.991	1.04 (0.25-2.29)	0.956
GG vs. AG vs. AA						0.868
AG+GG	60 (25.53)	110 (23.76)	1.10 (0.77-1.58)	0.606	1.08 (0.75-1.56)	0.680
AA+AG	232 (98.72)	457 (98.70)	1.00	1.00		
GG	3 (1.28)	6 (1.30)	0.99 (0.24-3.97)	0.983	1.02 (0.25-4.20)	0.976
G allele	63 (13.40)	116 (12.53)				
IL18R1 rs13015714 G>T						
GG	61 (25.96)	107 (22.96)	1.00	1.00		
GT	113 (48.09)	241 (51.72)	0.82 (0.56-1.21)	0.321	0.82 (0.55-1.21)	0.306
TT	61 (25.96)	118 (25.32)	0.91 (0.58-1.41)	0.664	0.91 (0.58-1.42)	0.679
TT vs. GT vs. GG						0.601
GT+TT	174 (74.04)	359 (77.04)	0.85 (0.59-1.22)	0.381	0.85 (0.59-1.22)	0.374
GG+GT	174 (74.04)	348 (74.68)	1.00	1.00		
TT	61 (25.96)	118 (25.32)	1.03 (0.72-1.48)	0.855	1.04 (0.73-1.50)	0.817
T allele	235 (50.00)	477 (51.18)				
IL18RAP rs917997 C>T						
CC	56 (23.93)	117 (25.27)	1.00	1.00		
CT	114 (48.72)	234 (50.54)	1.02 (0.69-1.50)	0.929	1.01 (0.68-1.50)	0.962
TT	64 (27.35)	112 (24.19)	1.19 (0.77-1.86)	0.432	1.20 (0.77-1.88)	0.429
TT vs. CT vs. CC						0.660
CT+TT	178 (76.07)	346 (74.73)	1.08 (0.75-1.55)	0.699	1.07 (0.74-1.55)	0.720
CC+CT	170 (72.65)	351 (75.81)	1.00	1.00		
TT	64 (27.35)	112 (24.19)	1.18 (0.83-1.69)	0.365	1.19 (0.83-1.71)	0.345
T allele	242 (51.71)	458 (49.46)				
IL28B rs8099917 T>G						
TT	217 (92.34)	421 (90.34)	1.00	1.00		
TG	18 (7.66)	45 (9.66)	0.78 (0.44-1.37)	0.384	0.79 (0.44-1.40)	0.416
GG	0 (0.00)	0 (0.00)	-	-	-	-
GG vs. TG vs. TT						0.383
TG+GG	18 (7.66)	45 (9.66)	0.78 (0.44-1.37)	0.384	0.79 (0.44-1.40)	0.416
TT+TG	235 (100.00)	466 (100.00)	1.00	1.00		
GG	0 (0.00)	0 (0.00)	-	-	-	-
G allele	18 (3.83)	45 (4.83)				

[a]Adjusted for age, sex, smoking status and alcohol consumption. *IL18*, interleukin 18; *IL18R1*, IL18 receptor 1; *IL18RAP*, IL18 receptor accessory protein; *IL28B*, interleukin 28B; GCA, gastric cardiac adenocarcinoma; OR, odds ratio; CI, confidence interval.

95% CI: 0.75-1.57, P=0.679); the GG genotype was not associated with the risk for GCA (GG vs. AA: adjusted OR=1.04, 95% CI: 0.25-2.29, P=0.956). In the dominant model, the *IL18* rs360719 AG/GG variants were not associated with the risk for GCA, compared with the *IL18* rs360719 AA genotype (adjusted OR=1.08, 95% CI: 0.75-1.56, P=0.680). In the recessive model, when the *IL18R1* rs13015714 AA/AG genotypes were used as the reference group, the GG homozygote genotype was not associated with risk for GCA (adjusted OR=1.02, 95% CI: 0.25-4.20, P=0.976) (Table III). No association was observed between the *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms and the risk for GCA (Table III).

Discussion

This study was conducted to demonstrate the associations of *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP*

rs917997 C>T and *IL28B* rs8099917 T>G with the susceptibility to GCA in a high-risk Chinese population. Our findings revealed that the variants *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G were not associated with the risk for GCA.

IL18 promotes cell death and tumor progression by activation of immune response and NK cells and may be used in anticancer gene therapy. *IL18* rs360719 polymorphism leads to loss of the OCT-1 transcription factor binding site. *IL18RAP* rs917997 C>T was found to be strongly associated with susceptibility to coeliac disease (23). *IL18RAP* rs917997 C>T was a protective factor in T1D (24). *IL18RAP* rs917997 C>T in the 3'-untranslated region of *IL18RAP* has been associated with decreased gene expression in the peripheral blood (25). *IL28B* rs8099917 T>G polymorphism has been associated with the response to IFN-γ-based antiviral therapy during the natural course of hepatitis C virus infection and after liver transplantation (26,27). In the present study, no significant associations with GCA were observed.

The frequencies of genetic polymorphisms often vary between ethnic groups (36). In the present study on Chinese subjects, the allele frequency of *IL18* rs360719 G was 0.125 among the 476 control subjects, which is consistent with that of the Chinese Han (0.142) and the African American populations (0.152), but significantly lower compared with that of the European population (0.292) in the SNP database. The allele frequency of *IL18R1* rs13015714 T was 0.512 among the 476 control subjects, which is consistent with that of the Chinese Han population (0.547), but significantly lower compared with that of the European (0.796) and Sub-Saharan African populations (0.894) in the SNP database. Similarly, the allele frequency of *IL18RAP* rs917997 T was 0.495 among the 476 control subjects, which is consistent with that of the Chinese Han population (0.488), but significantly higher comapred with that of the European (0.208) and Sub-Saharan African populations (0.049). Finally, the allele frequency of *IL28B* rs8099917 G was 0.048 among the 476 control subjects, which is consistent with that of the Chinese Han population (0.035), but significantly lower compared with that of the European (0.167) and Mexican populations (0.310) in the SNP database (http://www.ncbi.nlm.nih.gov/SNP).

Several limitations must be addressed in this case-control study. First, the patients and controls were enrolled from hospitals and may not represent the general population. Second, the moderate sample size limited the statistical power of our study, particularly in stratification analyses, and further well-designed two-stage fine-mapping studies are required to confirm our findings. Third, detailed information on cancer metastasis and survival were not available, which restricted further analyses on the role of *IL18R1* rs13015714 G>T and *IL18RAP* rs917997 C>T polymorphisms in GCA progression and prognosis.

In conclusion, our study provides evidence that *IL18* rs360719 A>G, *IL18R1* rs13015714 G>T, *IL18RAP* rs917997 C>T and *IL28B* rs8099917 T>G polymorphisms do not contribute to the risk of GCA. However, the power of our analysis was low, with a limited sample size, therefore allowing us to draw only preliminary conclusions. Future larger studies including other ethnic populations are required to confirm our findings.

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