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Polymorphisms of *IL-23R* predict survival of gastric cancer patients in a Chinese population

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ABSTRACT

IL-17/IL-23 pathway has been hypothesized to play a role in occurrence and progression of gastric cancer. To investigate the susceptibility and prognostic value of polymorphisms in genes in the IL-17/IL-23 pathway to gastric cancer, we performed a case-control study combined a retrospective study in a Chinese population. The Sequenom's MassARRAY® genotyping platform was used to genotype the polymorphisms, and infection of *Helicobacter pylori* (*H. pylori*) was determined by using a commercial *H. pylori* immunogold testing kit. The results showed that *IL-17A* rs3748067 T allele carriers have a higher gastric cancer risk than non-carriers in the subgroup of individuals with age > 64 years old (CT/TT *vs.* CC: adjusted OR = 1.55, 95% CI = 1.04–2.29). The result of prognosis shown that *IL-23R* rs1884444 GG and rs6682925 CC genotype were associated with unfavorable survival (rs1884444 GG *vs.* GT/TT: adjusted HR = 1.40, 95%CI:1.02–1.93; rs6682925 CC *vs.* CT/TT: HR = 1.43, 95%CI:1.06–1.92), respectively. The stratified analysis revealed that the significant association of rs1884444 was maintained in the subgroup of older than 64 years old, and that rs6682925 was associated with unfavorable survival in the subgroup of female and patients received chemotherapy. In short, we concluded two polymorphisms (rs1884444 and rs6682925) in *IL-23R* were associated with prognosis of gastric cancer patients.

1. Introduction

Gastric cancer remains a public health burden worldwide due to its high incidence and poor prognosis [1]. Currently, although the incidence has steadily declined, it's prognosis remains poor with low 5-year survival rate less than 30% [2]. Gastric cancer is a complex and heterogeneous disease and more than 90% cases are gastric adenocarcinomas, which was divided into gastric cardiac adenocarcinomas and non-cardiac adenocarcinomas by location. Epidemiologic studies have suggested that genetic background, *Helicobacter pylori* (*H. pylori*) infection, and behavioral factors (dietary, drinking, and smoking habits) are established risk factors of developing gastric cancer. Moreover, the incidence of gastric cancer has geographic heterogeneity, and more than half of gastric cancer cases worldwide occurs in East Asia, and eastern Asian countries with high rates, predominantly in China, may be attributed to the differences in genetic polymorphism distribution and prevalence of *H. pylori* infection [3].

Of the risk factors, *H. pylori* has been identified as a group I carcinogen, with more than half of the global human population is estimated to be infected. Also, the preventive effect of *H. pylori* eradication therapy on gastric cancer has been confirmed by clinical trials [4,5]. Published articles have revealed that *H. pylori* could promote the development of gastric cancer by several mechanisms [6], of which, inflammation of host response to *H. pylori* infection has been proved to involve in pathogenesis of gastric cancer, and genetic polymorphisms in immune-related genes, such as *IL-1B*, *IL-1RN*, *TNF-A* and *IL-10*, were reported to be the risk of gastric cancer [7,8]. We also previously reported genetic polymorphisms the promoter of *IL-1B/IL-1RN* were the risk of gastric cancer [9,10]. IL-17, a pro-inflammatory cytokine, is produced by T helper 17 (Th17) cell in response to their stimulation with IL-23 and induces the production of many other cytokines (such as IL-6, IL-1β, TGF-β, TNF-α). It is a central player in immunity at the sites most exposed to microorganisms [11], and IL-17 + γδ T cells (γδ17 T cells), the main providers of IL-17A, contribute to protective immune

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responses to infectious organisms [12]. Moreover, the interleukin-23 receptor (IL-23R) plays a vital role in the IL-23/IL-17 inflammatory signal transduction pathway [13], which was reported to be involved in the pathology of cancers [14]. Therefore, the polymorphisms occurring the gene of IL-17/IL-23 pathway could affect their expression, which were associated with cancer susceptibility [15–18] and prognosis of patients [19,20]. Although, the susceptibility of the some of polymorphisms harboring in the genes of IL-17/IL-23 pathway to the risk of cancers has been discussed previously, there was still no study systematically investigated the risk of these polymorphisms to gastric cancer risk, and the prognostic role of these polymorphisms in survival time of gastric cancer patients was still unknown. Based on the current knowledge of IL-17/IL-23 pathway involving in the pathology of gastric cancer and prognosis of patients, we performed a case-control study to assess the susceptibility of polymorphisms in genes of IL-17/IL-23 pathway to risk of gastric cancer in a Chinese population, and the prognostic value the polymorphisms for gastric cancer was also evaluated by a retrospective study.

2. Materials and methods

2.1. Study population

A total of 479 patients histologically diagnosed as gastric cancer and 483 age- and sex-matched healthy controls were recruited in this study. The health controls were those who came to the hospital for routine physical examination. Demographic features of health controls were collected via a questionnaire, and the clinical features of patients were collected from the patients' medical records. All the participants were Han race. For patients, the TNM stages were classified according to American Joint Commission for Cancer Staging in 2002, the sixth edition. The state of survival was obtained through on-site interview, direct calling or medical chart review. The Institutional Review Board of the Nanjing First Hospital approved protocol of this study, and written informed consents were obtained from all participants.

2.2. DNA extraction and genotyping

We retrieved the potential genetic variations from the National Center for Biotechnology Information dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP), and then the potential genetic variations were selected followed the following criteria: (1) the minor allele frequency (MAF) is not less than 5% in Han Chinese population; (2) with position in exons, promoter region, 5′ untranslated regions (UTR) or 3′ UTR; and (3) published results shown to be associated with any cancer risk. Finally, ten polymorphisms were selected (Table S1).

The DNA extraction and genotyping was performed as we previously described [21]. In brief, DNA was extracted using Gold Mag-Mini Whole Blood Genomic DNA Purification Kit according to the manufacture's protocol (GoldMag Co. Ltd. Xi'an, China), and the genotyping was performed on the Sequenom MassARRAY platform.

2.3. H. pylori infection detection

To identify the *H. pylori* infection, a commercial *H. pylori* immunogold testing kit (KangmeiTianhong Biotech (Beijing) Co., Ltd, Beijing, China) were used to detect *H. pylori* antibody according to the suggested procedures. The kit has been validated with sensitivity of 98.29% and specificity of 98.51% for the detection of *H. pylori* infection in Chinese population.

2.4. Statistical analysis

The difference of demographic features of the two groups was assessed by *t* test or $\chi 2$ test. A goodness of fit chi-square test was adopted to test the Hardy-Weinberg equilibrium (HWE) in the control group. The susceptibility of polymorphisms to gastric cancer risk was expressed with odds ratios (OR) and 95% confidence intervals (CIs), which were calculated using a logistic regression model based on SAS (v9.1; SAS Institute, Cary, NC, USA). Survival curves were assessed by Kaplan-Meier analysis. The association between the survival time and genetic variations was estimated with the log-rank test. The hazard ratios (HRs) of genotypes to patients' survival were calculated by Cox regression analysis with SPSS 11.0 (SPSS, Chicago, IL, USA). The p value < 0.05 was considered statistically significant difference.

3. Result

3.1. Characteristics of the study population

The demographic and exposure data of all participants are summarized in Table S2. There were no significant differences between the two groups with respect to age and gender distributions (age: $p = 0.748$; gender: $p = 0.881$). The frequency of *H. polyri* infection, cigarette smoking and alcohol consumption in cases was significantly higher than those in controls (*H. polyri*: $p = 0.039$; cigarette smoking: $p < 0.001$; alcohol consumption: $p < 0.001$), respectively.

The observed frequencies of all tested genotypes in controls did not deviate from HWE (shown in Table S1). The genotype distributions of the polymorphisms in cases and controls are presented in Table S3.

3.2. Association between polymorphisms and risk of gastric cancer

There was no significant difference of genotype distribution of all enrolled polymorphisms between the cases and controls. Logistic regression revealed that no polymorphism was associated with gastric cancer risk, shown in Table S3.

Due to the ratio of cigarette smoking and alcohol consumption in patients is significantly different from that in controls, we performed a logistic regression analysis for individuals having no habit of smoking or drinking, and the result shown that risk of enrolled polymorphisms to gastric cancer was consistent to that of all enrolled participants, shown in Table S4.

To further assess the susceptibility of enrolled polymorphisms to risk of gastric cancer, we performed a stratified analysis by age, gender, *H. pylori* infection status, tumor stage, and tumor site. The results revealed that *IL-17A* rs3748067 T allele carriers have higher gastric cancer risk than non-carriers in the subgroup of individuals with age > 64 years old (CT/TT *vs.* CC: adjusted OR = 1.55, 95%CI = 1.04–2.29), shown in Table S5. However, there is no significant association among the subgroup of patients with different pathological characteristics, shown in Table S6.

3.3. Association between polymorphisms and clinical outcome

A total of 460 patients were traced for follow-up information on survival period up to five years. For the characteristics of patients, there was no significant OS of patients among the subgroup of age, gender, tumor site, and chemotherapy treatment; however, patients in clinical stage III-IV have an unfavorable survival compared with those in clinical stage I-II (HR = 5.72, 95%CI: 4.11–7.96), and those patients accepted surgical treatment have favorable OS (HR = 0.33, 95%CI: 0.25–0.45), shown in Table 1.

For polymorphisms, *IL-23R* rs1884444 GG and rs6682925 CC genotype were associated with unfavorable survival (rs1884444 GG *vs.* GT/TT: adjusted HR = 1.40, 95%CI:1.02–1.93; rs6682925 CC *vs.* CT/TT: HR = 1.43, 95%CI:1.06–1.92), respectively, shown in Fig. 1 (see Table 2).

The stratified analysis based on the age, gender, tumor site, clinical stage, surgical treatment and chemotherapy were performed to evaluated the association between potential polymorphisms and OS, and the results shown that the significant association of rs1884444 to

Table 1
Association of characteristics and clinical features and overall survival of patients.

Characteristic	Cases, n	Death, n (%)	Log-rank P value	HR (95% CI)
Age				
≤64	224	130 (0.58)		Reference
> 64	236	156 (0.66)	0.077	1.23 (0.98, 1.56)
Gender				
Female	122	72 (0.59)		Reference
Male	338	214 (0.63)	0.230	1.18 (0.90, 1.54)
H. pylori infection				
Positive	251	148 (0.59)		Reference
Negative	209	138 (0.66)	0.162	1.18 (0.94, 1.49)
Clinical stage				
T1-T2	159	42 (0.26)		Reference
T3-T4	301	244 (0.81)	< 0.01	5.72 (4.11, 7.96)
Tumor site				
Cardiac	328	199 (0.61)		Reference
Non-cardiac	132	87 (0.66)	0.377	1.12 (0.87, 1.44)
Chemotherapy				
No	190	111 (0.58)		Reference
Yes	270	175 (0.65)	0.364	1.12 (0.88, 1.42)
Surgical treatment				
No	67	59 (0.88)		Reference
Yes	393	227 (0.58)	0.000	0.33 (0.25, 0.45)

unfavorable survival was maintained in the subgroup of older than 64 years old (adjusted HR = 1.68, 95%CI: 1.13–2.51), patients accepted chemotherapy (adjusted HR = 1.45, 95%CI: 1.00–2.12), and that rs6682925 was associated with unfavorable survival in the subgroup of female (adjusted HR = 1.96, 95%CI: 1.09–3.53), shown in Table 3.

4. Discussion

This case-control study included 479 patents and 483 control observed *IL-17A* rs3748067 T allele was associated with gastric cancer risk for those individuals older than > 64 years old. The survival analysis revealed that *IL-23R* rs6682925 and rs1884444 were associated with poor survival of patients, respectively.

Polymorphism rs3748067 locates the 3′UTR of *IL-17A*, and the rs3748067 T allele was previously reported as a risk of gastric cancer in Chinese population [22–24], which was consistent the result of this study in the older age subgroup; however, the conclusion was no always consistent [24]. We observed the significant association in the subgroup of older age but not in all cases and controls, indicating the risk may be modified by the interaction of the polymorphism and environment. Moreover, the data of dbSNP and published studies shown that rs3748067 T was the minor allele in worldwide; however, several studies reported rs3748067 C was the minor allele in Chinese population [25–28], which may be the origin of the published inconsistent results.

In the prognosis analysis, the log-rank test for the association of characteristics and clinical features and overall survival of patients revealed that clinical stage and surgical treatment have significantly effect on the survival time of patients, and results were consistently in that the clinical stage is a key part of deciding the best treatment, and patients in clinical stage T3-T4 have less likely to accept surgical treatment and have shorter survival time than those in T1-T2.

For the polymorphism and prognosis, we observed that *IL-23R* rs1884444 and rs6682925 were associated with the unfavorable OS of patients; however, after adjusted for characteristics and clinical features of patients, the significant association was not maintained. In addition, subgroup analysis revealed that the significant association was maintained in the subgroup of female and patients accepting chemotherapy, indicating the prognosic value of rs6682925 for gastric cancer patients may be modified by the patients characteristics. The polymorphism rs6682925 locates at 5′ flanking region, and it was previously reported to be associated with survival of non-small-cell lung cancer [29], which was consistent our result. In addition, it was reported that subjects carrying rs6682925TC and CC genotypes had significantly increased mRNA level of IL-23R in PBMCs than those with TT genotype [30]. In

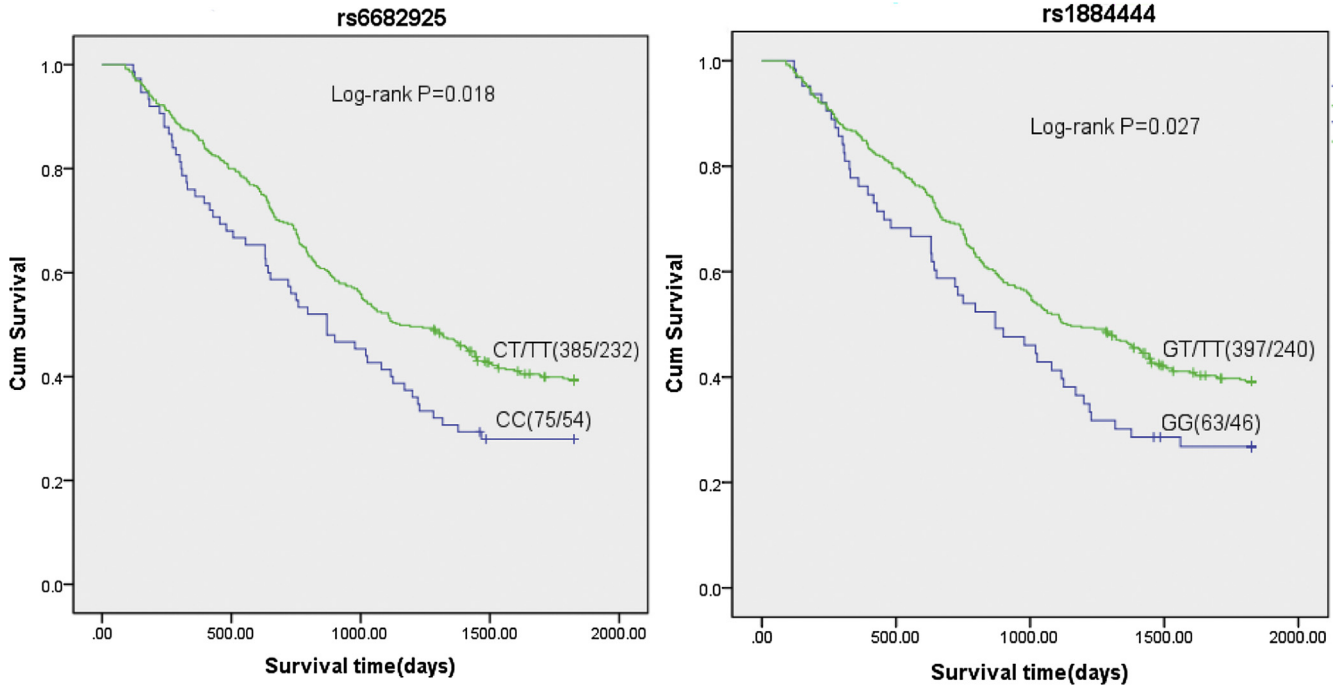

Fig. 1. Kaplan-Meier survival curves for gastric cancer patients by recessive model. Overall survival of rs6682925 and rs1884444 in recessive model.

Table 2
Association between polymorphism and overall survival of gastric cancer patients in recessive model.

Polymorphism	Genotype	Cases	Death, n(%)	Log-rank P value	HR (95% CI)	Adjusted HR (95% CI) [a]
rs8193036	CT/CC	427	267 (62.5)		Reference	
	TT	33	19 (57.6)	0.440	0.83 (0.52, 1.33)	0.67 (0.42, 1.07)
rs2275913	GA/GG	358	226 (63.1)		Reference	
	AA	102	60 (58.8)	0.713	0.95 (0.71, 1.26)	1.14 (0.85, 1.52)
rs3748067	CT/CC	447	280 (62.6)		Reference	
	TT	13	6 (46.2)	0.272	0.64 (0.28, 1.43)	0.87 (0.38, 1.97)
rs763780	CT/TT	451	280 (0.62)		Reference	
	CC	9	6 (0.67)	0.780	1.12 (0.50, 2.52)	1.13 (0.50, 2.56)
rs9382084	GT/TT	398	247 (0.62)		Reference	
	GG	62	39 (0.63)	0.841	0.97 (0.69, 1.35)	0.94 (0.67, 1.33)
rs6682925	CT/TT	385	232 (0.60)		Reference	
	CC	75	54 (0.72)	**0.018**	**1.43 (1.06, 1.92)**	1.27 (0.94, 1.71)
rs1884444	GT/TT	397	240 (0.60)		Reference	
	GG	63	46 (0.73)	**0.027**	**1.43 (1.04, 1.96)**	**1.40 (1.02, 1.93)**
rs17375018	GA/GG	418	255 (61)		Reference	
	AA	42	31 (73.8)	0.059	1.43 (0.98, 2.08)	1.29 (0.89, 1.88)
rs10889677	CA/AA	424	261 (0.62)		Reference	
	CC	36	25 (0.69)	0.537	1.14 (0.76, 1.72)	1.43 (0.95, 2.16)
rs11209032	AG/GG	354	221 (0.62)		Reference	
	AA	106	65 (0.61)	0.763	0.96 (0.73, 1.26)	0.95 (0.72, 1.25)

[a] Adjusted for age, sex, tumor site, TNM stage, surgical treatment, chemotherapy. Bold represents any values with $P < 0.05$.

Table 3
Subgroup analyses of association between polymorphisms in *IL-23R* and gastric cancer survival in recessive model.

		Case, n	Death, n (%)	rs6682925		rs1884444	
Subgroup				CT/TT:CC	Adjusted HR (95% CI) [a]	GT/TT:GG	Adjusted HR (95% CI) [a]
Age	< 64	224	130 (0.58)	192:32	1.19 (0.74, 1.92)	198:26	1.07 (0.62, 1.85)
	≥64	236	156 (0.66)	193:43	1.37 (0.93, 2.03)	199:37	**1.68 (1.13, 2.51)**
Gender	Male	338	214 (0.63)	282:56	1.10 (0.78, 1.56)	293:45	1.33 (0.91, 1.94)
	Female	122	72 (0.64)	103:19	**1.96 (1.09, 3.53)**	104:18	1.62 (0.89, 2.94)
T	T1-T2	159	42 (0.26)	141:18	0.99 (0.38, 2.55)	142:17	1.37 (0.57, 3.30)
	T3-T4	301	244 (0.81)	244:57	1.24 (0.90, 1.69)	255:46	1.28 (0.91, 1.81)
Site	Cardiac	132	87 (0.66)	109:23	1.51 (0.90, 2.54)	114:18	1.46 (0.83, 2.57)
	Non-cardiac	328	199 (0.61)	276:52	1.16 (0.80, 1.67)	283:45	1.41 (0.96, 2.08)
Chemotherapy	No	190	111 (0.58)	158:32	1.01 (0.62, 1.64)	163:27	1.28 (0.77, 2.11)
	Yes	270	175 (0.65)	227:43	**1.45 (1.00, 2.12)**	234:36	1.49 (0.99, 2.45)
Surgical treatment	No	67	59 (0.88)	51:16	1.75 (0.95, 3.21)	53:14	1.81 (0.95, 3.45)
	Yes	393	227 (0.58)	334:59	1.14 (0.81, 1.61)	344:49	1.32 (0.91, 1.91)

[a] Adjusted for age, sex, tumor site, TNM stage, surgical treatment, chemotherapy. Bold represents any values with $P < 0.05$.

this study, unfortunately, we failed to analysis the association between *IL23R* expression and survival of patients. Instead of it, we used an online web tool (http://kmplot.com/analysis/index.php) to analysis the relation of *IL23R* expression and survival of gastric cancer patients [31], and result of two studies shown that higher expression of *IL23R* was potentially associated with unfavorable survival (Affy ID: 1552912, $p = 0.089$; Affy ID: 1561853, $p = 0.0034$) (see Affiliated figure 1), which was consistent to the result of our study. Thus, this study suggested that rs6682925 CC associated with increased *IL23R* expression predicts unfavorable survival of gastric cancer patients. To our knowledge, this is first study reporting rs6682925 CC could serve as a predictive marker for survival of gastric cancer patients.

rs1884444 is a missense variant at exon 2 inducing a replacement of histidine (H) with glutamine (Q) at codon 3. It was reported to contribute the susceptibility of hepatocellular carcinoma [32], esophageal cancer [33]; however, the protective factor was also reported for intestinal-type gastric cancer. In this study, we failed to find any significant association of this polymorphism to gastric cancer risk, but we observed rs1884444 GG genotype was associated with poor survival, and the significant association maintained in the subgroup of those with older age, suggesting its prognosis value may be limited in a certain population. Whereas, the function of this polymorphism remains unclear and thus the predictive role rs1884444 in prognosis of gastric cancer patients should be confirmed by further functional and association study.

rs10889677 is a polymorphism in the 3′-UTR of *IL-23R*, suggesting that it could enhance *IL-23R* mRNA and protein expression by disturbing the binding capacity of let-7e and let-7f [34]. Previous study concluded it as a risk factor of gastric cancer [35]; however, in this study, no significant association of the polymorphism with gastric cancer risk was found, which was consistent to the result of meta-analysis [36]. To date, there is no study reporting the susceptibility of rs10889677 to gastric cancer risk and it's predictive value for prognosis of gastric cancer patients. To our knowledge, this is the first study discussed the predictive role of *IL-23R* polymorphism in survival of gastric cancer patients, therefore, the results of this study should be ascertain by further larger sample sized study.

This study evaluated the polymorphisms in IL-17/IL-23 pathway as risk and prognostic factor for gastric cancer. Some limitations of this study should be addressed. Firstly, the number of patients enrolled this study was not large enough, which may limit the statistical power; moreover, in the stratified analysis, the significant association between polymorphisms and survival time could not be maintained, which may be due to the limited sample size in the subgroup. Secondly, several potential environmental factors, such as diet, history of gastric diseases, were not included in this study, which may influence gastric cancer risk. Thirdly, although we adopted the data format online database to confirm the significant association between *IL23R* expression and

survival of patients, this study failed to detect the protein level to support the association between genetic variations and survival of patients. Finally, there are number of polymorphisms occurring in the IL-17/IL-23 pathway, here we selected ten of them based on our enrolled criteria, but their functions were largely unclear.

In short, we concluded the two polymorphisms (rs1884444 and rs6682925) in *IL23R* were associated with prognosis of gastric cancer patients.

Conflicts of interest

We declare that we have no competing interests.

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Author contributions

B.H and S.W conceived the idea. B.H, Y.P and B.P performed the experiment. X.W, L.Z, H.S and X.X designed and analyzed the data. S.W supervised the overall project. B.H, Y.P and X.L wrote the manuscript with suggestions from all the other co-authors.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.01.014.

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