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Research Paper

Complement Receptor 1 Genetic Variants Contribute to the Susceptibility to Gastric Cancer in Chinese Population

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Abstract

As the receptor for C3b/C4b, type 1 complement receptor (CR1/CD35) plays an important role in the regulation of complement activity and is further involved in carcinogenesis. This study aimed to elucidate the association of *CR1* genetic variants with the susceptibility to gastric cancer in Chinese population. Based on the NCBI database, totally 13 tag single nucleotide polymorphisms (SNPs) were selected by Haploview program and genotyped using iPlex Gold Genotyping Assay and Sequenom MassArray among 500 gastric cancer cases and 500 healthy controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression to evaluate the association of each SNP with gastric cancer. Of all selected Tag SNPs , CR1 rs9429942 T > C was found to confer to the risk of developing gastric cancer. Compared with the carriers with rs9429942 TT genotype, those with CT genotype had 88% decreased risk of developing gastric cancer with OR (95%CI) of 0.12 (0.03-0.50). Generalized multifactor dimensionality reduction (GMDR) analysis revealed a significant three-way interaction among rs75422544 C > A, rs10494885 C > T and rs7525160 G > C in the development of gastric cancer with a maximum testing balance accuracy of 56.07% and a cross-validation consistency of 7/10 (P = 0.011). In conclusion, our findings demonstrated the genetic role of *CR1* gene in the development of gastric cancer in Chinese population.

Key words: Complement receptor 1; gastric cancer; genetic variant; single nucleotide polymorphism.

Introduction

Gastric cancer remains the fourth most common cancer and the second leading cause of cancer-related mortality worldwide, contributing to a significant burden of disease, particularly in developing countries [1]. Epidemiological studies have identified many risk factors for gastric cancer, such as *Helicobacter pylori* infection, high intake of salt-preserved foods, tobacco smoking and pernicious anemia [2]. However, only a fraction of individuals exposed to these factors develop gastric cancer during their lifetime, which suggests that genetic susceptibility plays an important role in gastric carcinogenesis.

The complement system is a collection of serum proteins that are integral to inflammatory processes and to innate immune responses to infection. Based on the epidemiological and experimental data, it has been established that chronic inflammation is involved in tumor onset, promotion and progression [3, 4]. Over recent years, studies have suggested an insidious relationship between gastric cancer and

chronic inflammation, especially resulting from the infection with *Helicobacter pylori* [5, 6]. Chronic inflammation orchestrates a tumor-supporting microenvironment that is an indispensable participant in the neoplastic process [7]. Considering the connection of complement system, innate immunity and chronic inflammation, complement proteins may play an important role in carcinogenesis. Studies have suggested that complements facilitate innate immune against cancer through direct tumor lysis or complement-independent cytotoxicity (CDC) [8]. Studies have indicated that complement C5a in the tumor microenvironment promoted tumor growth by the myeloid-derived suppressor (MDS) cell-mediated immunosuppression [9, 10]. Taken as a whole, the complement system may have a dual effect on the process of carcinogenesis [11].

Complement receptor 1 (CR1/CD35) is a type I membrane-bound glycoprotein that belongs to the regulators of complement activity (RCA) family [12, 13]. Acting as the receptor for C3b and C4b, CR1 expressed on various cell types, including lymphocytes, erythrocytes, phagocytes, and dendritic cells [14]. As an inhibitor of complement activation, *CR1* has been reported to be involved in the pathogenesis of several cancers [15, 16].

Previously, we investigated 13 tag SNPs in *CR1* gene and found that rs7525160 polymorphism was significantly associated with the susceptibility to non-small cell lung cancer (NSCLC) [17]. In this study, we performed a case-control study in a Chinese population to test the hypothesis that the tag SNPs of *CR1* contribute to the susceptibility to gastric cancer.

Materials and Methods

Study subjects

The present case-control study comprised 500 patients with gastric cancer and 500 healthy controls Patients were recruited between Jan 2008 and Dec 2013 from Hebei United University affiliated Tangshan Gongren Hospital and Tangshan Renmin Hospital in China, without receiving any radiotherapy or chemotherapy at the time of recruitment and no restrictions in regard to age, gender. The response rate for patients was 94%. All subjects were genetic unrelated Han Chinese. The eligible patients were primary histopathologically confirmed and previously untreated by radiotherapy and chemotherapy. Patients with previous malignancy or metastasized cancer from other organs were excluded. The controls were randomly selected from cancer-free population from the community conducted in the same region during the same period when patients were recruited. The selection criteria for the controls included no prior history of malignancy, and control subjects were frequency-matched to the patients by age (±5 years) and gender. At recruitment, written informed consent was obtained from each subject. This study was approved by the Institutional Review Board of Hebei United University.

Selection of Tag SNPs and SNP genotyping

Based on the Chinese population data from HapMap database, we used HaploView 4.2 program to select the candidate tag SNPs with an r^2 threshold of 0.8 and minor allele frequency (MAF) greater than 1%. Under this criteria, totally 11 tag SNPs were selected. Additionally, we added two potential functional SNPs, rs9429942 and rs6691117 [18, 19]. Therefore, we included 13 SNPs in our study, which represents common genetic variants in Chinese population.

Genotyping was performed at Bomiao Tech (Beijing, China) using iPlex Gold Genotyping Assay and Sequenom MassArray (Sequenom, San Diego, CA, USA). Sequenom's MassArray Designer was used to design PCR and extension primers for each SNP. The PCR primers used are available upon request. Genotyping quality control consisted of no-temple control samples for allele peaks and verifying consistencies in genotype calls of 2% randomly selected duplicate samples. In addition, two control samples were included on each plate as genotyping controls for inter-plate reproducibility. Hardy-Weinberg Equilibrium (HWE) was also evaluated in unrelated controls.

Statistical analysis

Statistical analyses were performed using SPSS16.0 statistical software package (version16.0, SPSS, Chicago, IL). The chi-square goodness of fit test was used for any deviation from Hardy–Weinberg equilibrium in controls. The χ^2 test was used to examine the differences in demographic distributions and genotype frequencies between cases and controls. We estimated the cancer risk associated with CR1 tag SNPs by odds ratios (ORs) and 95% confidence intervals (CIs) computed by logistic regression model adjusted for age, gender, and smoking status. All statistical tests were two-sided and differences were taken as significant when *P*-value was < 0.05. Gene-gene and gene-smoking interactions were analyzed by open resource generalized multifactor dimensionality reduction (GMDR) software package (version 0.9) and Quanto [20, 21]. For given sample size, the power to detect statistically significant associations was calculated using online power and sample size calculator for unmatched case-control study (http://www.stat.ubc.ca).

Results

Subject characteristics

The frequency distributions of selected characteristics of participants were shown in Table 1. No significant statistical differences in the sex (P = 0.407), age (P = 0.317) and smoking status (P = 0.652) distributions were observed between cases and controls, which suggesting that the frequency matching was adequate.

Association of individual Tag SNP and gastric cancer risk

Table 2 showed the position and minor allele frequency (MAF) of 13 tag SNPs of CR1 in HapMap database among Chinese population. Besides the rs9429782 polymorphism, the genotype distributions of other 12 SNPs in controls accorded with Hardy-Weinberg equilibrium (P > 0.05). Therefore, we excluded the rs9429782 from further analysis. As depicted in Table 3, these 12 tag SNPs were genotyped in all subjects including the 500 patients with gastric cancer and 500 healthy controls. The genotype frequency of rs9429942 T>C among the cases was significantly different from those among controls (χ^2 = 10.415, P = 0.001). There was no statistical difference of genotype distributions between gastric cancer cases and healthy controls for other 11 tag SNPs (P > 0.05). Multivariate logistic regression analysis was used to assess the association of 12 tag SNPs of *CR1* with the risk of gastric cancer (Table 3). For rs9429942 T>C polymorphism, the CT genotype was significantly associated with a decreased risk of gastric cancer (OR = 0.12; 95% CI = 0.03-0.50; P = 0.004) compared with the homozygote TT. Based on our sample size, our study had 93% power to detect the significant association of rs9429942 polymorphism with the risk of cancer risk with OR of 0.12. For rs7525160 G>C variant, when compared with GG genotype, CG genotype was associated with a decreased risk of gastric cancer (OR = 0.7; 95% CI = 0.53-0.93; P = 0.013); but CC genotype was not (OR = 1.13; 95% CI = 0.80-1.62; P = 0.485). For other 10 tag SNPs of *CR1*, our data did not show any association with the susceptibility to gastric cancer in our study population (P>0.05). When stratified by smoking status, our results did not show any interaction of Tag SNPs of *CR1* with smoking status contribute to the risk of developing gastric cancer (data not shown).

Association of SNP-SNP interactions and gastric cancer risk

GMDR was used to evaluate gene-gene interaction of 12 SNPs from *CR1* gene (Table 4). Although the SNP rs7525160 in *CR1* had the highest testing balanced accuracy of 54.88% among 12 SNPs, the result was not significant (P = 0.055). Similarly, the rs4844600 G>A and rs10494885 C>T were shown to be the best two-way model with a testing balance accuracy of 52.92%, however, the interaction was not significant (P = 0.055). Three-way interaction model among rs75422544 C>A, rs10494885 C>T and rs7525160 G>C showed the maximum testing balance accuracy (56.07%) and cross validation consistency (7/10). The three-way interaction was significant (P = 0.011).

Table 1. Distributions of selected characteristics in cases and control subjects

Variables	Cases (n=500)		Controls (n=500)		
	No	(%)	No	(%)	P^a
Sex					0.407
Male	357	71.4	344	68.8	
Female	143	28.6	156	31.2	
Age					0.317
≤50	141	28.2	156	31.2	
51-60	149	29.8	157	31.4	
>60	210	42.0	187	37.4	
Smoking status					0.652
Non-smoker	294	58.8	302	60.4	
Smoker	206	41.2	198	39.6	

[a]Two-sided χ^2 test.

Table 2. Primary information of genotyped SNPs of CR1

Gene and locus	Rs number	Contig position	Location	Base change	MAF in controls	*P* for HWE test	Calling rate (%)
CR1 1q32	rs7525160	1186193	5′ near gene	G/C	0.42	0.910	100
	rs9429942	1186409	5′ near gene	T/C	0.02	0.928	99.3
	rs9429782	1187134	5′ near gene	G/T	0.24	<0001	100
	rs4844600	1197086	E60D	G/A	0.39	0.999	100
	rs6656401	1209828	Intron	G/A	0.04	0.720	99.9
	rs3886100	1256906	Intron	A/G	0.48	0.420	99.7
	rs11118167	1299933	Intron	T/C	0.14	0.992	99.4
	rs6691117	1300710	I2065V	A/G	0.17	0.920	99.5
	rs3818361	1302747	Intron	C/T	0.37	0.923	100
	rs7542544	1304002	Intron	C/A	0.49	0.623	100
	rs2296160	1313099	I2419A	C/T	0.37	0.579	99.6
	rs17048010	1318668	Intron	T/C	0.20	0.986	99.0
	rs10494885	1332968	3′near gene	C/T	0.39	0.960	99.5

MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Table 3. Genotype frequencies of CR1 among cases and controls and their association with gastric cancer

CR1 Genotypes	Controls (n=500)		Cases (n=500)		OR (95% CI)[a]	*P* value
	No	(%)	No	(%)		
rs7525160						
GG	167	33.4	189	37.8	1.00 (ref.)	
CG	248	49.6	199	39.8	0.70(0.53-0.93)	0.013
CC	85	17.0	112	22.4	1.13(0.80-1.62)	0.485
rs3886100						
GG	124	24.8	129	25.8	1.00 (ref.)	
AG	235	47.0	260	52.0	1.06 (0.78-1.44)	0.711
AA	141	28.2	111	22.2	0.77 (0.54-1.09)	0.135
rs11118167						
TT	371	74.2	377	75.4	1.00 (ref.)	
CT	119	23.8	109	21.8	0.91(0.67-1.23)	0.530
CC	10	2.0	14	2.8	1.32(0.58-3.02)	0.513
rs10494885						
CC	187	37.4	172	34.4	1.00 (ref.)	
CT	240	48.0	236	47.2	1.05(0.80-1.38)	0.735
TT	73	14.6	92	18.4	1.40(0.96-2.03)	0.079
rs7542544						
CC	136	27.2	109	21.8	1.00 (ref.)	
AC	239	47.8	260	52.0	1.33(0.98-1.81)	0.069
AA	125	25.0	131	26.2	1.29(0.91-1.84)	0.155
rs6691117						
AA	344	68.8	347	69.4	1.00 (ref.)	
AG	143	28.6	138	27.6	0.97(0.73-1.28)	0.807
GG	13	2.6	15	3.0	1.11(0.52-2.38)	0.786
rs6656401						
GG	465	93.0	475	95.0	1.00 (ref.)	
AG	35	7.0	25	5.0	0.70(0.41-1.19)	0.183
rs2296160						
CC	193	38.6	214	42.8	1.00 (ref.)	
CT	244	48.8	230	46.0	0.86(0.66-1.12)	0.269
TT	63	12.6	56	11.2	0.81(0.54-1.23)	0.327
rs9429942						
TT	483	96.6	498	99.6	1.00 (ref.)	
CT	17	3.4	2	0.4	0.12(0.03-0.50)	0.004
rs4844600						
GG	184	36.8	199	39.8	1.00 (ref.)	
AG	239	47.8	242	48.4	0.94(0.72-1.23)	0.644
AA	77	15.4	59	11.8	0.72(0.49-1.08)	0.110
rs3818361						
CC	197	39.4	210	42.0	1.00 (ref.)	
CT	237	47.4	235	47.0	0.93(0.72-1.22)	0.618
TT	66	13.2	55	11.0	0.80(0.53-1.20)	0.282
rs17048010						
TT	317	63.4	318	63.6	1.00 (ref.)	
CT	163	32.6	162	32.4	0.99(0.77-1.29)	0.940
CC	20	4.0	20	4.0	1.01(0.53-1.91)	0.985

[a]Data were calculated by unconditional logistic regression and adjusted for gender, age and smoking status.

Table 4. Summary of GMDR SNP-SNP interaction results for CR1 gene

Models	Training Bal. Acc (%)	Testing Bal. Acc. (%)	*P* value	Cross-validation Consistency
Rs7525160	54.90	54.88	0.055	10/10
Rs4844600, rs10494885	56.67	52.92	0.055	5/10
Rs7542544, rs10494885, rs7525160	59.27	56.07	0.011	7/10

GMDR, generalized multifactor dimensionality reduction; Training Bal. Acc, training balance accuracy; Testing Bal. Acc, testing balance accuracy.

Discussion

Genetic background plays an important role in the development of gastric cancer, which is a multi-factorial genetic disease resulting from gene-environment interaction [22]. Over recent years, genome-wide association studies (GWAS) have identified multiple genetic loci associated with gastric cancer risk [23-25]. In addition, much effort in case–control studies has been spent in searching for cancer susceptibility genes, such as genes coding for inflammatory mediators [7], DNA repair [26], apoptosis [27] and carcinogen metabolism [28]. In a *Nature Immunology* article, Rutkowski and his colleges reviewed that complement proteins might facilitate the process of carcinogenesis by increasing activity of mitogenic signaling pathways, inducing cellular proliferation, and promoting immunosupression [29]. Acting as a negative regulator of the complement cascade, CR1 was also involved in the development of various cancers. In the present study, we investigated the association of 13 tag SNPs of *CR1* with the risk of gastric cancer in Chinese population and found that rs9429942 CT genotype was associated with a decreased risk of gastric cancer (OR = 0.12; 95% CI = 0.03-0.50; $P = 0.004$), compared with the TT genotype. Furthermore, GMDR analysis revealed that a three-loci significant interaction among rs75422544, rs10494885 and rs7525160 of *CR1* gene with the highest test accuracy of 56.07% ($P = 0.011$). To the best of our knowledge, it is first report that *CR1* genetic variations contribute to the risk of developing gastric cancer.

Gastric cancer is characterized by a prominent inflammatory component [30]. As a fundamental component of innate immunity, complement is an enzymatic cascade that results in the release of pro-inflammatory anaphylatoxins, including most notably the anaphylatoxins C3a and C5a [31, 32]. Complement system has long been thought to fight against cancer by exerting the effects of immunosurveillance in the immunologic microenvironment of tumors [10]. However, tumor cells are protected from complement-mediated injury by membrane-bound complement regulatory proteins (mCRPs) that are often up-regulated on tumor cells [33-35]. These mCRPs consists of CR1, complement factor H (CFH), decay accelerating factor (DAF, CD55), membrane cofactor protein (MCP, CD46), and homologous restriction factor 20 (HRF29, CD59), which can inhibit complement activation by blocking the complement cascade at the C3 activation stage or preventing formation of the membrane attack complex (MAC) [33, 36]. Therefore, it is desirable to combine anti-tumor monoclonal antibodies (mAb) immunotherapy or tumor vaccines with the blocking of mCRPs in cancer

immunotherapy [37]. Considering the important role of mCRPs in carcinogenesis, it is reasonable that genetic variants in mCRPs might affect the susceptibility to certain cancers. For instance, recent evidence has showed that *CFH* Y402H polymorphism interacted with cigarette smoking to effect the development of lung cancer in the Chinese population [38]. Studies also showed that the CR1 3650A>G Rsa I polymorphism in exon 22 was associated with the risk of gallbladder cancer [16] and the rs7525160 G>C polymorphism contributed to the risk of non-small cell lung cancer [17].

In the present study, we provided the evidence that the CT genotype of *CR1* rs9429942 was strongly associated with protective effect against gastric cancer in Chinese population. As depicted in the table 2, rs9429942 T>C variant located in 5′ near *CR1* gene. Teeranaipong *et al* evaluated the association of rs9429942 T>C variant with the erythrocyte CR1 expression level in 24 healthy Thai subjects and found that TT genotype contribute to higher erythrocyte CR1 level [18]. The lower expression may effect on the rate of clearance of immune complexes from circulation[39]. The concentration of immune complexes in advanced gastric cancer patients was significantly higher than that in normal subjects[40]. This may explain the role of rs9429942 in the development of gastric cancer. However, the function of rs9429942 T>C variant still need be verified in large study. Whatever, these studies at least illustrated that *CR1* rs9429942 might be a good candidate genetic susceptibility locus for certain diseases. Meanwhile, we also paid attention to another interesting result that the CG genotype of *CR1* rs7525160 was significantly associated with a decreased risk of gastric cancer compared with homozygote GG, while the CC genotype was not. Based on the current data, rs7525160 G>C can not be considered as a risk factor for gastric cancer. However, in our previous study, we reported that rs7525160 CC and CG genotype were related to an increased risk of developing NSCLC in Chinese population [17]. The discrepancy may result from the different tumor site, therefore more convincing studies still need be done in the future.

Based on our findings, we could speculate about the role of the *CR1* gene for the pathogenesis of gastric cancer. As a receptor for C3b/C4b, CR1 functioned both as a regulator of complement activation and as a vehicle for immune complexes (ICs) clearance [41]. By reversibly binding to C3b and C4b and further inactivating C3 and C5 covertases, CR1 involved in the classical and alternate pathway [42]. In addition, CR1 serves as a necessary cofactor in the proteolytic cleavage of C3b and C4b by complement factor I (CFI) [43]. The genetic variations in *CR1* gene has been reported to affect CR1 copy number on erythrocytes, which in turn correlates with the rate of ICs clearance from the circulation [39, 44].

Considering the ubiquity of genetic interactions in the pathogenesis of complex diseases, the identification and characterization of susceptible genes or polymorphisms require a thorough understanding of gene-gene interactions [45]. Over recent years, gene-gene interaction factors have been taken into account in studies of gastric cancer carcinogenesis [46, 47]. In our study, multiple interactions of genetic variants, including rs75422544, rs10494885 and rs7525160 were observed for gastric cancer. This desirable result would encourage us to explore genetic susceptibility conferred by co-stimulatory molecules in gastric cancer in the future.

In conclusion, our data provided the new evidence of the role of *CR1* in the development of gastric cancer. However, some limitations should be addressed. Due to the relatively small sample size, further study still need to be conducted to confirm the findings of the present study. Furthermore, the biological functions of *CR1* polymorphism also need to be investigated.

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Competing Interests

The authors have declared that no competing interest exists.

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