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BRIEF ARTICLE

Association between polymorphism rs6983267 and gastric cancer risk in Chinese population

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Abstract

AIM: To explore the association between single nucleotide polymorphisms (SNPs) at 8q24 and gastric cancer risk.

METHODS: A case-control investigation including 212 gastric cancer patients and 377 healthy controls was conducted. The genotypes of SNPs (rs6983267, rs7008482 and rs10808555) were examined and established through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Multivariate logistic regression models were used to evaluate the association between SNPs and gastric cancer.

RESULTS: The genotype frequencies of rs6983267 in gastric cancer patients were obviously different from those in the control (P = 0.005). GT genotype of rs6983267 was associated with an increased risk of gastric cancer compared with GG genotype (adjusted odds ratio = 2.01, 95% confidence interval: 1.28-3.14). Further stratified analysis indicated that rs6983267 GT genotype facilitated the risk of gastric cancer of non-cardiac and intestinal type (OR: 2.638, 95% CI: 1.464-4.753; OR: 1.916, 95% CI: 1.166-3.150, respectively).

CONCLUSION: This study demonstrates for the first time that rs6983267 is involved in susceptibility to gastric cancer, although further large-sample investigations are still needed.

Key words: Gastric cancer; Genetic susceptibility; Single nucleotide polymorphism; MYC; 8q24

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INTRODUCTION

Gastric cancer is the second most common cause of death

from cancer in the world[1] and the incidence rate was 16.2 per 100 000[2]. Despite of a marked decrease in gastric cancer mortality rate in many countries, there is a higher prevalence of gastric cancer in the Chinese population than in other races. No doubt, either a high absolute number or a high mortality of gastric cancer has become a key public health issue in China.

Although numerous biological and epidemiological studies have shown risk factors for gastric cancer, the available knowledge is still insufficient to reveal the exact mechanism of gastric cancer. Current researches have shown that both genetic and environmental factors play an important role in gastric carcinogenesis[3,4] and genetic susceptibility accounts for 35% of disease etiology[5]. Recently, the association between variants at 8q24 and breast, prostate and colorectal cancers has been discovered and confirmed by several research groups[6-15], which suggested a complex contribution of polymorphisms at 8q24 to the formation of multiple adenomas. However, whether these common variants in 8q24 are also associated with the risk of gastric cancer has so far not been published.

In the present study, we conducted a case-control association study to evaluate the effect of rs6983267, rs7008482 and rs10808555 in 8q24 in the risk of gastric cancer in the Chinese population.

MATERIALS AND METHODS

Subjects

A total number of 216 cases and 400 controls were enrolled from January 2009 to January 2010 in Tongji Hospital, Shanghai. Among the 1360 subjects who were invited to take part in this study, only 45% individuals agreed to participate and donated 3 mL venous blood sample. All the gastric cancer cases had been checked by the gastroscopy and diagnosed by the specialized physician. The exclusion criteria of cases included: (1) Having a history of any other cancers or any metastasized cancer (carcinomas were not originally from stomach); and (2) Having undergone radiotherapy or chemotherapy. Controls were randomly selected among the first-visit outpatients who were confirmed to have no cancer or a prior history of neoplasm. Available baseline characteristics, including age, gender, race, tumor location, histological type, were recorded. All the subjects were genetically unrelated ethnic Han Chinese. This study was approved by the institutional review board of Tongji University School of Medicine. Written informed consent was obtained from all participants.

Genotyping

According to the manufacturer's protocol, we used Flexi Gene DNA Kit (Qiagen, Hilden, Germany) to extract genomic DNA from peripheral blood leukocytes of the subjects and stored extracted DNA at -20℃. Unique primer sequences were designed in the website of primer3 (http://frodo.wi.mit.edu/primer3/input.htm) and primer sequences for rs6983267, rs7008482 and rs10808555 were as follows: 5'-ATGAAGGCGTCGTCCAAATGA-3' (forward) and 5'-TTGGCTGGCACTGTCTGTATA-3' (reverse); 5'-CCAAGCAGAGAGGAACCAACT-3' (forward) and 5'-GCCACCCTTTATTCTCCAACC-3' (reverse); 5'-ATATGGTCCCTGCCCTCAAG-3' (forward) and 5'-CACTGTGCTAAAGGAATCAGCAA-3' (reverse), respectively. Polymorphisms genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Amplification reactions were carried out in a total volume of 15 μL containing 0.3 mmol/L of each deoxynucleoside triphosphate, 10 mmol/L Tris-HCl, 50 mmol/L KCl, 2 mmol/L $MgCl_2$, 20% Q solution (Qiagen, Hilden, Germany), 0.16 μmol/L of each primer, 10 ng genomic DNA, and 1 U Taq (TaKaRa, Otsu, Shiga, Japan). Cycling conditions were: 94℃ for 3 min, followed by 10 cycles of 94℃ for 30 s, 64℃ for 30 s with a 0.5℃ decrement of the annealing temperature per cycle and 72℃ for 30-45 s, followed by 30 cycles of 94℃ for 30 s, 59℃ for 30 s and 72℃ for 30 s, followed by 72℃ for 8 min. PCR products were digested overnight at 37℃ with a predicted restriction enzyme, Tsp45I (Fermentas, Vilnius, Lithuania) for rs6983267, CviQI (Fermentas, Vilnius, Lithuania) for rs7008482, Eco130I (Fermentas, Vilnius, Lithuania) for rs10808555 and were analyzed on 3% agarose with ethidium bromide staining. Three sorts of PCR products were digested into 3 different types of fragments. For rs6983267, the G allele resulted in two fragments of 198-bp and 344-bp, and the C allele produced one fragment of 498-bp. For rs7008482, the G allele resulted in two fragments of 270-bp and 131-bp, while the T allele produced one fragment of 401-bp. For rs10808555, the G allele digested into two fragments of 193-bp and 110-bp, and the A allele generated one fragment of 303-bp.

All the samples were assayed blindly without knowing the case or control status. After genotyping was performed, two research assistants read the gel pictures independently. When they failed to reach a consensus on the tested genotypes (< 1%), they would repeat the genotyping again so as to achieve a final consensus. To ensure the genotyping accuracy, randomly selected PCR products were reevaluated by DNA sequencing[16]. In addition, 5% of all samples were randomly selected and genotyped in duplicate, and the results were 100% concordant.

Statistical analysis

Hardy-Weinberg equilibrium was tested using the two-sided χ^2. χ^2 test was used to compare genotype frequency and demographic distributions between cases and controls. Multivariate unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for the association between genotypes and gastric cancer, adjusting for age and gender. The co-dominant and the dominant models were used for the analysis. In the co-dominant model, each SNP was separated into three categories, 1 for each genotype, with one genotype chosen as the reference group. For the dominant model, each SNP was modeled as a dichotomous variable with

Table 1 Characteristics of cases and control

Variables	Gastric cancer *n* (%)	Control *n* (%)	*P* value[2]
Overall	212	377	
Sex			0.063
Male	152 (71.7)	242 (64.2)	
Female	60 (28.3)	135 (35.8)	
Age			0.670
Mean ± SD (yr)	62.47 ± 11.6	62.89 ± 11.3	
Histological types			
Intestinal	155 (73.1)		
Diffuse	44 (20.8)		
Mixed	13 (6.1)		
Tumor location[1]			
Cardia	74 (38.5)		
Noncardia	118 (61.5)		

[1]The number of subjects in cases for tumor location (n = 192) was less than the total number (n = 212) because some information was not obtained; [2]Two-sided χ^2 test for the frequency distribution of variants between gastric cancer cases and controls.

1 genotype chosen as the reference group, and the other two genotypes combined into one category. All tests were two-sided and P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 16.0 software package (SPSS, Chicago, IL)

RESULTS

Demography

Among 216 gastric cancer cases and 400 controls, 4 cases and 23 controls were dropped out due to poor-quality genomic DNA. Of the 212 cases of gastric cancer, 155 were intestinal type, 44 diffuse type and 13 mixed-type. The mean age of cases was 62 years and the mean age of controls was 63 years. The characteristics of the cases and controls are summarized in Table 1. There was no significant difference between the groups with respect to the age and gender distributions.

SNPs and gastric cancer risk

Among the controls, the genotype distributions of rs6983267 and rs7008482 were in Hardy-Weinberg equilibrium (P > 0.1 and P > 0.9, respectively), but rs10808555 did not fit Hardy-Weinberg equilibrium (P < 0.05). The genotype frequencies of rs6983267 were obviously different between gastric cancer patients and control (χ^2 = 10.8, P = 0.005). Analysis under both co-dominant model and dominant model showed that only rs6983267 was significantly associated with gastric cancer risk, after adjustment for age and gender (Table 2). In the co-dominant model, rs6983267 GT genotype was associated with approximately 2 times higher odds of gastric cancer risk (OR: 2.01, 95% CI: 1.28-3.15) compared with the GG genotype. In the dominant model, combined genotypes (GT + TT) of rs6983267 were significantly associated with increased risk of gastric cancer in comparison with GG genotype (OR: 1.82, 95% CI: 1.18-2.81). However, the genotype frequencies of rs7008482 were similar between gastric cancer patients and controls (P > 0.05).

Table 2 Association between variation in single nucleotide polymorphisms rs6983267 and rs708482 and risk of gastric cancer

Genotype	Control *n* (%)	Cases *n* (%)	*P* value
rs6983267			
GT/TT	268 (72.8)	166 (83.0)	0.007
TT	72 (19.6)	32 (16.0)	0.369
GT	196 (53.3)	134 (67.0)	0.002
GG	100 (27.2)	34 (17.0)	
rs7008482			
GT/GG	224 (61.0)	142 (67.0)	0.138
GG	52 (14.2)	38 (17.9)	0.108
GT	172 (46.9)	104 (49.1)	0.250
TT	143 (39.0)	70 (33.0)	

Furthermore, we evaluated the contributions of SNPs to subgroups according to age, gender, different histological types and tumor locations (Table 3). In the subgroup aged ⩽ 60 years, rs6983267 GT genotype markedly increased the risk of gastric cancer referring to GG genotype (OR: 3.21, 95% CI: 1.52-6.68), but in the subgroup aged > 60 years, no significant difference was found (P = 0.137). In addition, rs6983267 GT genotype was significantly associated with augmentation of gastric cancer risk in both male and female. As to the histological types and tumor sites, rs6983267 GT heterozygote had a significantly increased risk for non-cardiac gastric cancer (OR: 2.64, 95% CI: 1.46-4.75) and intestinal-type gastric cancer (OR: 1.92, 95% CI: 1.17-3.15) in contrast with GG genotype. Further analysis in Table 4 demonstrated that rs6983267 GT genotype increased the risk of an intestinal-type gastric adenocarcinoma from non-cardiac region. For rs7008482, only GG genotype was associated with significantly increasing risk of gastric cancer compared with TT genotype in male subgroup (OR: 1.88, 95% CI: 1.01-3.47) (Table 3).

DISCUSSION

This is the first study to discover the association between rs6983267 at 8q24 and the susceptibility of gastric cancer, although other previous studies had reported that rs6983267 was associated with the risk of colorectal cancer and prostate cancer[13,17]. Our observation and analysis indicated that compared with GG genotype of rs6983267, GT genotype and combined genotypes (GT + TT) were both markedly associated with the increasing risk for gastric cancer. And further stratified investigation confirmed that rs6983267 GT genotype facilitated the risk of non-cardiac and intestinal-type gastric cancer. Therefore, rs6983267 is a novel gastric cancer associated polymorphism in 8q24 in Chinese Han population.

Rs6983267 resides at 8q24, proximal to a processed pseudogene, *POU5F1P1*, which is a retrotransposed copy of the POU-domain transcription factor Oct4[18]. At least one mouse *Oct4* pseudogene has been shown to mediate stem cell regulatory function[19], suggesting that *Oct4*

Table 3 Association between rs6983267 and rs7008482 polymorphism and clinicopathological features of gastric cancer

	rs6983267							rs7008482						
	GG	GT			TT			TT	GT			GG		
	HC/GC	HC/GC	OR (95% CI)	*P* value	HC/GC	OR (95% CI)	*P* value	HC/GC	HC/GC	OR (95% CI)	*P* value	HC/GC	OR (95% CI)	*P* value
Age (yr)														
≤ 60	46/11	76/59	3.21 (1.52-6.77)	0.002	29/13	1.86 (0.73-4.72)	0.191	66/30	71/46	1.42 (0.80-2.51)	0.230	15/11	1.61 (0.66-3.92)	0.295
> 60	54/23	120/75	1.54 (0.87-2.74)	0.137	43/19	1.05 (0.50-2.16)	0.901	77/40	101/58	1.15 (0.69-1.90)	0.592	37/27	1.44 (0.77-2.70)	0.258
Sex														
Male	60/26	125/94	1.77 (1.04-3.02)	0.036	48/23	1.10 (0.56-2.17)	0.783	98/46	107/77	1.52 (0.96-2.41)	0.072	32/29	1.88 (1.01-3.47)	0.045
Female	40/8	71/40	3.68 (1.49-9.06)	0.005	24/9	2.22 (0.73-6.74)	0.160	45/24	65/27	0.83 (0.42-1.65)	0.599	20/9	0.98 (0.38-2.54)	0.967
Histological types														
Intestinal	100/26	196/98	1.92 (1.17-3.15)	0.010	72/23	1.20 (0.63-2.28)	0.571	143/52	172/73	1.17 (0.77-1.78)	0.047	52/30	1.56 (0.89-2.72)	0.118
Diffuse	100/7	196/25	1.93 (0.80-4.66)	0.144	72/8	1.74 (0.60-5.09)	0.309	143/15	172/23	1.36 (0.68-2.71)	0.390	52/6	1.26 (0.46-3.47)	0.651
Mixed	100/1	196/11	5.56 (0.71-44.52)	0.103	72/1	1.37 (0.08-21.06)	0.827	143/3	172/8	2.29 (0.63-9.43)	0.228	52/2	1.95 (0.34-13.47)	0.474
Location														
Cardia	100/16	196/40	1.26 (0.67-2.38)	0.469	72/14	1.18 (0.54-2.58)	0.681	143/25	172/35	1.18 (0.67-2.07)	0.574	52/14	1.52 (0.73-3.18)	0.263
Noncardia	100/16	196/82	2.64 (1.46-4.75)	0.001	72/12	1.06 (0.47-2.38)	0.888	14/39	172/59	1.28 (0.81-2.04)	0.295	52/20	1.47 (0.78-2.77)	0.228

Multivariate unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for the association between genotypes and gastric cancer, adjusting for age and gender. HC: Health control; GC: Gastric cancer.

Table 4 Stratified analysis of rs6983267 genotypes and gastric cancer

	Control *n* (%)	Intestinal case		Diffuse case	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Cardia					
TT	72 (19.6)	12 (22.2)	1.243 (0.53-2.90)	1 (8.3)	0.44 (0.04-4.31)
GT	196 (53.3)	29 (53.7)	1.131 (0.56-2.28)	8 (66.7)	1.36 (0.35-5.28)
GG	100 (27.1)	13 (24.1)		3 (25)	
Noncardia					
TT	72 (19.6)	8 (9.6)	0.99 (0.38-2.59)	4 (16.7)	1.91 (0.44-8.25)
GT	196 (53.3)	64 (77.1)	2.95 (1.49-5.86)	16 (66.6)	2.56 (0.80-8.17)
GG	100 (27.1)	11 (13.3)		4 (16.7)	

pseudogene may exert influence in regulating stem cell proliferation[7]. *Oct4* also plays a critical role in maintaining stem cell pluripotency[20], self-renewal, and lineage commitment[21]. *Oct4* has been found to promote tumor growth in a dose-dependent manner[22] and epithelial dysplasia by interfering with progenitor cell differentiation[23]. Although the expression of many *Oct4* pseudogenes in poorly differentiated tumors[24] has been observed, the related molecular mechanism in cancer is unknown.

On the other hand, rs6983267 is located in the region which is 335 kb away from the nearest gene, *MYC*. MYC is able to increase the growth and proliferation of normal gastric cells[25], and may enhance the canceration of gastric epithelial cells by regulating a variety of genes related to proliferation, differentiation[26], and apoptosis[27]. MYC overexpression has been described in over 40% of gastric cancer (in both intestinal- and diffuse-type gastric adenocarcinoma)[28]. Overexpression of *MYC* gene can influence some biological characteristics of normal gastric cells, directly regulate the genes involved in cell cycle regulation[29], such as *cyclin A, cyclin B* and *cdk4*[30], and accelerate cancerous growth ultimately. The promotion of the growth and proliferation of these cells helps tumor cells maintain malignant phenotype. Moreover, the therapeutic medicine inhibits gastric cancer cell growth by suppressing *MYC* gene expressions, which consistently confirms the crucial function of MYC in gastric cancer cell growth[31]. The region harboring rs6983267 is a transcriptional enhancer and differentially binds transcription factor 7-like 2 (TCF7L2) due to rs6983267, leading to a different physi-

cal interaction with *MYC*[32]. Given that the cancer risk-associated SNP enhances the expression of *MYC* through increased distal enhancer activity[32,33], it is reasonable to speculate that rs6983267 may alter expression of *MYC* through modifying regulatory sequences in this region. Despite the research progress, further studies are needed about the concrete molecular mechanisms of the joint effect between *MYC* and rs6983267 polymorphism.

Previous studies have demonstrated that rs6983267 is possibly related to some kinds of malignant tumor. In the present study we found that rs6983267 is a novel gastric cancer related polymorphism. Stratified analysis indicated that the associations between rs6983267 GT genotype and gastric cancer tended to vary with tumor sites and histological types. Rs6983267 GT genotype was associated with both intestinal and non-cardiac type of gastric cancer but not associated with the diffuse and cardiac type, and increased the risk of intestinal type among the non-cardiac gastric cancer, which suggested that rs6983267 GT genotype is more important in modulating the intestinal and non-cardiac type of gastric cancer. However, TT genotype in rs6983267 tended to be a protective factor in intestinal type among the non-cardial gastric cancer although this was not significant in the association analysis. This phenomenon could be explained, because distinct clinical, epidemiological and molecular features have been noted among tumors arising from cardia or non-cardia, and among intestinal or diffuse histological subtypes[34]. For instance, the loss of p16 and smad4 protein expression and the positive *EPstein-Barr virus* (*EBV*) status are more frequent in cardiac carcinomas than that in non-cardiac carcinomas reported by Kim *et al*[35]. Lu *et al*[36] reported that intestinal-type gastric cancer predominates in high-risk geographic areas, especially in Japan, Korea and China, whereas the diffuse-type gastric cancer has a uniform geographic distribution. The observed differences between gastric cancers in tumor location and histological types suggest that they are distinct diseases with different etiologies[37]. Thus, various genetic factors, including rs6983267, may be involved in different subtypes of gastric cancer (cardiac or non-cardiac; intestinal or diffuse). Another plausible explanation for this situation may be the genetic heterogeneity which may limit the ability to detect an association between TT genotype and gastric cancer. Other variants, which have a strong association with risk of gastric cancer, including as yet undiscovered susceptibility genes, may affect the outcome of this research. Moreover, the limited sample size may be not sufficient to generate this association. Overall, the genetic susceptibility and environmental factors have been proposed to play an important role in the etiology of gastric cancer, and different subtypes of gastric cancer may have diverse biological mechanisms.

Apart from the discovery in rs6983267, this study failed to demonstrate the association between rs7008482 and the risk of gastric cancer, although rs7008482 was reported to be associated with prostate and colorectal cancer[10,11]. Nevertheless, positive association between rs7008482 GG genotype and risk of gastric cancer in male subgroup has been shown. Rs7008482 lies within an intronic region of the *NSMCE2* (also called *MMS21*) gene, and MMS21 protein is a SUMO ligase which is required for DNA replication, recombination and repair[11]. Considering the function of *NSMCE2* gene and MMS21 protein, we wonder whether the limited sample size hampered the detection of association between rs7008482 and gastric cancer risk. Therefore, further studies are still needed to confirm it.

In conclusion, our data demonstrated for the first time that rs6983267 may predispose to the susceptibility of gastric cancer, especially the intestinal and non-cardiac type. However, as the sample size of the present study is relatively small, additional tests of variant at 8q24 for its association with gastric cancer in a larger population, and functional studies of MYC and other nearby genes will be required to fully understand the mechanisms of the cancer-specific risk at 8q24.

COMMENTS

Background

Gastric cancer (GC) is one of the most common cancers, and the second most frequent cause of cancer-related deaths in the world. Epidemiological studies have shown that genetic factors play a crucial role in gastric carcinogenesis. Recently, common polymorphisms located at chromosome 8q24 have been identified to increase the tumor risk. The authors investigated the associations between rs6983267 polymorphisms and GC risk.

Research frontiers

Chromosome 8q24 is an established risk locus for many common epithelial cancers. Polymorphism rs6983267 is a susceptibility marker for prostate and colon cancers, and perhaps also ovarian and other cancers. The relationship between rs6983267 polymorphism and GC needs to be addressed.

Innovations and breakthroughs

To our knowledge, this is the first study of GC risk variant at 8q24 in a Chinese population. Polymorphism rs6983267 was found to be associated with an increased risk of GC, which had been not reported before. The result of stratified analysis according to histological types confirms the contribution of rs6983267 in non-cardiac and intestinal type of gastric carcinogenesis.

Applications

These findings might be of value in the explanation of gastric carcinogenesis. They could to be used for further investigations about the association between genetic predisposition and the risk of GC at 8q24.

Terminology

MYC is an oncogene, the protein encoded by this gene is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and proliferations. Single nucleotide polymorphism is a DNA sequence variation occurring when a single nucleotide-A, T, C, or G-in the genome (or other shared sequence) differs between members of a species or paired chromosomes in an individual.

Peer review

The authors investigated the association of the 3 single nucleotide polymorphisms (SNPs) (rs6983267, rs7008482 and rs10808555) with the risk of gastric cancer by a case-control study, and found that GT genotype of rs6983267 was associated with an increased risk of gastric cancer compared with GG genotype (AOR = 2.01, 95% CI: 1.28-3.14). After stratification, rs6983267 GT genotype was associated the risk of non-cardiac and intestinal type of gastric cancer. This study provides some new SNP for the evaluation of gastric cancer risk.

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