Association analysis of colorectal cancer susceptibility variants with gastric cancer in a Chinese Han population

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ABSTRACT. Evidence suggests that some genetic variants are risk factors for both colorectal cancer (CRC) and gastric cancer (GC). Thus, we selected 12 reported single nucleotide polymorphisms (SNPs) from genome-wide association studies of CRC and conducted this case-control study to assess the associations between these SNPs and the risk for GC in a southern Chinese population. All SNPs were genotyped in 249 individuals with GC and 292 healthy population-matched subjects using the Sequenom MassArray iPLEX System. Association analyses based on the χ^2 test and binary logistic regression were performed to determine the odds ratio (OR) and 95% confidence interval (95%CI) for each SNP. A stratified analysis by gender was also performed. Borderline significant associations were observed for rs4444235 (P = 0.070) and rs10411210 (P = 0.084), both fitting the overdominant model. The rs4444235 CT genotype showed a protective

effect (OR = 0.72, 95%CI = 0.50-1.03), while the rs10411210 CT genotype was a risk factor (OR = 1.40, 95%CI = 0.96-2.05) as compared with the CC+TT genotype. In the female subgroup, the rs6983267 GT genotype (compared with TT, OR = 2.31, 95%CI = 1.07-4.99) and the rs10505477 CT genotype (compared with TT, OR = 2.36, 95%CI = 1.09-5.11) significantly increased the risk for GC. No significant association was detected for the other SNPs. These results provide evidence that known genetic variants associated with CRC risk may also confer risk for GC.

Keywords: Single nucleotide polymorphism; Susceptibility; Gastric Cancer; Colorectal cancer;

INTRODUCTION

Gastric cancer (GC) is a global public health concern, ranking as the fourth leading cause of cancer mortality, with a 5-year survival rate of only 20% (Crew and Neugut, 2006). Several risk factors have been identified through epidemiological studies for GC, including *Helicobacter pylori* infection, low fiber intake, and tobacco smoking (Epplein et al., 2008; Ladeiras-Lopes et al., 2008). Environmental exposure and genetic susceptibility are also thought to contribute to GC risk (Tan et al., 2012). The accumulation of specific genetic alterations, including polymorphisms, contributes to gastric tumorigenesis (González et al., 2002).

Single nucleotide polymorphisms (SNPs) have attracted considerable attention in recent years as potential markers for predicting disease susceptibility. Genome-wide association studies (GWAS) of many common genetic variants have examined different individuals to determine whether a variant is associated with a trait. This method has become a major strategy for identifying genetic susceptibility factors for polygenic diseases, including cancers.

Recently, a GWAS performed in a North-Central Chinese population identified 7 SNPs at loci 1q22 and 10q23 as being significantly associated with GC susceptibility (Abnet et al., 2010). However, GWAS have been criticized for consistently displaying a low effect size of SNPs with an apparently extremely significant P value.

Thus, the re-validation of GWAS-derived SNPs in different populations and different diseases has become an important addition to the discovery of new variants. Furthermore, SNP information regarding GC from GWAS is rather limited, particularly compared with colorectal cancer (CRC), another common gastrointestinal cancer.

Evidence suggests that some genetic variants are risk factors for both CRC and GC (Li et al., 2011, 2012). Based on this hypothesis, we traced some well-known colorectal cancer GWAS-identified SNPs with GC susceptibility to assess potential associations. Thus, in this study, 12 "hit" SNPs identified by CRC GWAS analysis were selected and then assessed to determine whether these SNPs are suitable markers for GC.

MATERIAL AND METHODS

Subjects

The samples used in this study were obtained from individuals visiting the outpatient

and inpatient clinics of the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi Province, China. The ethics committee of Southern Medical University approved this study and all subjects provided written informed consent.

A total of 249 GC patients and 292 healthy subjects were enrolled between 2009 and 2010. All diagnoses of GC were confirmed histologically. Control subjects were cancer-free individuals selected randomly from the hospital's outpatient department. The mean ages of the patients and the control subjects were 54.82 (standard deviation, SD = 12.47) and 58.65 (SD = 16.14) years, respectively. Additionally, among the 249 cases, 176 were adenocarcinomas by pathological type, 43 and 79 were cardiac cancers and non-cardiac cancers by tumor site, respectively, and 110 and 15 were lymph node metastases and distant metastases by tumor stage, respectively.

Selection of SNPs from colorectal cancer GWAS

Based on previous studies, we selected 8 commonly identified SNPs from GWAS: rs12701937, rs16892766, rs7014346, rs6983267, rs10505477, rs10795668, rs719725, and rs3802842 (Zanke et al., 2007; Tomlinson et al., 2007, 2008; Tenesa et al., 2008; Lascorz et al., 2010), and 4 (rs4444235, rs9929218, rs10411210, and rs961253) from meta-analyses based on GWAS data (Houlston et al., 2008) (Table 1).

Table 1. Genotype characteristics of 12 chosen colorectal cancer susceptibility variants.

No.	SNP	Chr.	Location/Nearest gene	Major allele	Minor allele	P
1	rs12701937	7p14.1	Intergenic/GLI3,INHBA	C	T	1.1×10^{-3}
2	rs16892766	8q23.3	Intergenic/EIF3H	A	-	3×10^{-18}
3	rs10795668	10p14	Intergenic/BC031880	G	A	3×10^{-13}
4	rs7014346	8q24.21	Intergenic/POU5FIP1, HsG57825, DQ515897	G	A	9×10^{-26}
5	rs6983267	8q24.21	Intergenic/MYC	T	G	7×10^{-11}
6	rs10505477	8q24.21	Intergenic/ORF DQ515897	C	T	3×10^{-11}
7	rs719725	9p24	Intergenic	A	C	2.3×10^{-2}
8	rs3802842	11q23	Intergenic/C11orf93	A	C	4×10^{-7}
9	rs4444235	14q22.2	Intergenic/BMP4	T	C	8×10^{-10}
10	rs9929218	16q22.1	Intron/CDH1	G	A	1×10^{-8}
11	rs10411210	19q13.1	Intron/RHPN2	C	T	5×10^{-9}
12	rs961253	20p12.3	Intergenic/BMP2	C	A	2×10^{-10}

Genotyping

Peripheral blood samples were drawn from participants at the First Affiliated Hospital of Nanchang University. Samples were delivered frozen by express mail to the School of Biotechnology, Southern Medical University, and stored at -70°C. Genomic DNA was extracted using a commercial blood DNA kit (Tiangen Biotech; Beijing, China) according to manufacturer instructions and stored at -70°C until required.

The 12 SNPs were genotyped using MassARRAY genotyping technology (Sequenom, Inc.; San Diego, CA, USA) according to manufacturer instructions. Primers were designed using proprietary software, Assay Design 3.1, provided by Sequenom Inc. The primer sequences are shown in **Table S1**.

Statistical analysis

Exclusion criteria for SNPs were as follows: 1) <85% genotype call rate, 2) minor allele frequency (MAF) < 5% in cases or controls, and 3) Hardy-Weinberg equilibrium exact P value < 0.05 in cases or controls; SNPs satisfying 1 or more of these criteria were excluded.

Genotype and allele frequencies were compared using chi-squared tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by a logistic regression analysis and adjusted for age and gender. Statistical analyses were performed using the web-based tool SNPstats (http://bioinfo.iconcologia.net/SNPstats). The results from this calculator were consistent with those obtained using the SPSS software (ver. 13.0; Solé et al., 2006). Gender stratification analysis was preformed after analysis. All statistical analyses were 2-tailed, and the significance level was set at 0.05.

RESULTS

Two SNPs (rs719725 and rs3802842) were excluded because their genotype call rates were <80%; the other SNPs passed the threshold. One SNP (rs16892766) was monomorphic and was excluded. The other 9 SNPs all passed the Hardy-Weinberg equilibrium exact test (P > 0.05) in cases and controls. MAFs in controls were similar to data of Han Chinese in Beijing (CHB) and Japanese in Tokyo (JPT) populations from HapMap (http://hapmap.ncbi.nlm.nih.gov/) (Table 2).

Table 2. Interethnic comparisons of minor allele frequencies for the 9 chosen SNPs in our subjects with HapMap data.

SNP/Allele	Minor allele	Present study (%)		Hapmap (%)			
		Control	Case	CHB	JPT	European	African
rs12701937	T	32.5	31.9	33.3	37.8	43.2	0
rs10795668	A	33.7	34.8	34.4	40	35.8	0.8
rs7014346	A	33.6	32.1	35.6	21.1	26.7	46.7
rs6983267	G	44	46.1	37.2	29.1	48.7	98.2
rs10505477	T	43.4	46.3	37.8	33.3	42.2	89.2
rs4444235	C	46.8	47.9	52.3	54.7	44.2	29.5
rs9929218	A	19.2	18	17.4	16.3	29.5	29.2
rs10411210	T	18	20.8	18.6	13.4	8.4	45.1
rs961253	A	6.9	8.4	5.8	18	40.3	32.3

CHB = Han Chinese in Beijing; JPT = Japanese in Tokyo.

The genetic models for inheritance evaluation were not significant for any SNP, but 2 SNPs (rs4444235 and rs10411210) showed borderline significance (P = 0.070 and P = 0.084, respectively), both fitting the overdominant model (Table 3). These results suggest a possible inverse association between the rs444235 CT genotype (OR = 0.72, 95%CI = 0.50-1.03) and a possible positive association of the rs10411210 CT genotype (OR = 1.40, 95%CI = 0.96-2.05) and GC risk as compared with the CC+TT genotypes.

A subsequent gender stratification analysis showed that in the female group, the rs6983267 GT genotype (compared with TT, OR = 2.31, 95%CI = 1.07-4.99) and the rs10505477 CT genotype (compared with TT, OR = 2.36, 95%CI = 1.09-5.11) significantly increased GC risk (Table 4).

Table 3. Distribution of 9 SNPs in gastric cancer and control groups.

SNP	Model	Genotype	Frequency N (%) Control	Frequency N (%) Case	Adjusted OR (95%CI)	P
rs12701937	Dominant	CC	124 (46.6%)	115 (48.3%)	Reference	
		CT	111 (41.7%)	94 (39.5%)	0.98 (0.67-1.43)	0.97
		TT	31 (11.7%)	29 (12.2%)	1.06 (0.60-1.87)	
rs10795668	Dominant	GG	123 (46.4%)	98 (41.9%)	Reference	
		AG	105 (39.6%)	109 (46.6%)	1.29 (0.88-1.89)	0.3
		AA	37 (14%)	27 (11.5%)	0.90 (0.51-1.59)	
rs7014346	Dominant	GG	119 (44.7%)	105 (44.3%)	Reference	
		GA	115 (43.2%)	112 (47.3%)	1.13 (0.78-1.64)	0.28
		AA	32 (12%)	20 (8.4%)	0.69 (0.37-1.28)	
rs6983267	Dominant	TT	74 (32.6%)	70 (28.5%)	Reference	
		GT	106 (46.7%)	125 (50.8%)	1.29 (0.84-1.97)	0.49
		GG	47 (20.7%)	51 (20.7%)	1.08 (0.64-1.82)	
rs10505477	Dominant	CC	75 (33%)	70 (28.9%)	Reference	
		CT	107 (47.1%)	120 (49.6%)	1.23 (0.80-1.88)	0.64
		TT	45 (19.8%)	52 (21.5%)	1.15 (0.68-1.95)	
rs4444235	Dominant	TT	71 (26.7%)	68 (28.8%)	Reference	
		CT	141 (53%)	110 (46.6%)	0.77 (0.51-1.18)	0.15
		CC	54 (20.3%)	58 (24.6%)	1.19 (0.72-1.97)	
	Overdominant	TT+CC	125 (47%)	126 (53.4%)	Reference	
		CT	141 (53%)	110 (46.6%)	0.72 (0.50-1.03)	0.07
rs9929218	Dominant	GG	174 (65.2%)	156 (66.1%)	Reference	
		GA	83 (31.1%)	75 (31.8%)	1.02 (0.70-1.50)	0.57
		AA	10 (3.8%)	5 (2.1%)	0.57 (0.19-1.72)	
rs10411210	Dominant	CC	181 (68%)	146 (61.3%)	Reference	
		TC	74 (27.8%)	85 (35.7%)	1.38 (0.94-2.02)	0.19
		TT	11 (4.1%)	7 (2.9%)	0.75 (0.28-2.00)	
	Overdominant	CC+TT	192 (72.2%)	153 (64.3%)	Reference	
		CT	74 (27.8%)	85 (35.7%)	1.40 (0.96-2.05)	0.087
rs961253	Dominant	CC	230 (86.5%)	200 (84%)	Reference	
		AC	35 (13.2%)	36 (15.1%)	1.16 (0.69-1.93)	0.61
		AA	1 (0.4%)	2 (0.8%)	2.69 (0.24-30.21)	

Table 4. Genotype distributions of rs6983267 and rs10505477 in male and female subjects respectively.

SNP	Model	Genotype	Male Control	Male Case	Male OR (95%CI)	Female Control	Female Case	Female OR (95%CI)
rs6983267	Dominant	TT	40 (30.3%)	57 (32.4%)	Reference	34 (35.8%)	13 (18.6%)	Reference
		GT	61 (46.2%)	81 (46.0%)	0.96 (0.57-1.63)	45 (47.4%)	44 (62.8%)	2.31 (1.07-4.99)
		GG	31 (23.5%)	38 (21.6%)	0.90 (0.48-1.70)	16 (16.8%)	13 (18.6%)	1.65 (0.61-4.45)
rs10505477	Dominant	CC	40 (30.3%)	57 (32.9%)	Reference	35 (36.8%)	13 (18.8%)	Reference
		CT	63 (47.7%)	77 (44.5%)	0.88 (0.52-1.50)	44 (46.3%)	43 (62.3%)	2.36 (1.09-5.11)
		TT	29 (22.0%)	39 (22.5%)	0.98 (0.52-1.85)	16 (16.8%)	13 (18.8%)	1.70 (0.63-4.58)

DISCUSSION

In the present study, we evaluated 12 SNPs identified by GWAS of CRC in an independent Chinese population of patients with GC. Among these SNPs, 1 (rs16892766) was monomorphic. Two SNPs (rs719725 and rs3802842) were excluded because they did not pass the threshold set. Two borderline-significant associations were observed between rs4444235 (P = 0.070) and rs10411210 (P = 0.084) and GC in the present population. Furthermore, gender-stratified analysis identified 2 SNPs (rs6983267 and rs10505477) that were significantly associated with GC in the female subgroup. No significant association was detected for the other SNPs.

Because we sought to identify novel GC risk-related variants from CRC GWAS, SNPs were not randomly chosen, but instead obtained from previous studies. Among these SNPs, rs6983267 at region 8q24 is an established risk locus for many common malignant cancers, such as prostate (Beuten et al., 2009), ovarian (White et al., 2010), breast (Fletcher et al., 2008), and gastric cancers (Lochhead et al., 2011; Guo et al., 2011), but not for colon cancer. It has been reported that rs6983267 showed a significant association with GC risk in a Chinese population (Guo et al., 2011). Another SNP at 8q24, rs10505477, which maps to approximately 5.86 kb centromeric to rs6983267 and has high linkage disequilibrium with rs6983267, was also reported to confer risk for CRC (Zanke et al., 2007) and ovarian cancer (Ghoussaini et al., 2008). This SNP has also been examined in GC, but no significant association has been reported (Lochhead et al., 2011; Guo et al., 2011). The SNPs rs6983267, rs7014346, and rs10505477 are also from the 8q24 region, which is a gene desert, but an established risk-associated locus in CRC and prostate cancer (Takata et al., 2010; Schumacher et al., 2011). Furthermore, 8q24 has also been reported to be associated with glioma (Shete et al., 2009), breast cancer (Easton et al., 2007; Turnbull et al., 2010; Fletcher et al., 2011), lymphoma, and leukemia (Crowther-Swanepoel et al., 2010; Enciso-Mora et al., 2010), bladder cancer (Kiemeney et al., 2008; Rothman et al., 2010), and ovarian cancer (Goode et al., 2010). The SNP rs12701937 (7p14.1) was first reported to be associated with CRC in German familial CRC cases. The SNP rs10795668 (10p14) was found to be associated with both CRC (Tomlinson et al., 2008) and a decreased risk of CRC recurrence in a Chinese population (Xing et al., 2011). The SNPs rs4444235 (14q22.2), rs961253 (20p12.3), rs9929218, and rs10411210 were identified from a meta-analysis (Houlston et al., 2008). For the other SNPs, only associations with CRC have been recognized. Because of the shared molecular mechanism(s) in carcinogenesis and cancer progression, we hypothesized that these CRC genetic variants would be associated with the risk of GC. In the current study, we successfully assessed 10 SNPs in 249 GC cases and 292 controls. Mechanistically, rs6983267 was hypothesized to confer risk for colorectal cancer (Pomerantz et al., 2009) and prostate cancer (Wasserman et al., 2010) by influencing MYC expression; however, negative evidence has also been reported (Prokunina-Olsson and Hall; 2009). The SNP rs4444235 showed *cis*-acting regulation of bone morphogenetic protein 4 (BMP4) (Lubbe et al., 2012), although the relevant mechanisms remain unknown. For the 2 8q24 SNPs, rs6983267 and rs10505477, which were previously identified in solid tumor-associated polymorphisms, we only observed a significant association with GC risk in females. Two previous similar studies reported different results. The SNP rs6983267 was found to be associated with GC risk in another Chinese population (Guo et al., 2011), with the GT genotype having a higher risk than the GG genotype. In contrast, a Caucasian population-based study showed no significant association between rs6983267 or rs10505477 and GC risk (Lochhead et al., 2011), reflecting a potentially population-specific effect. In addition, we found that rs16892766 was monomorphic with the AA genotype in our study group, which is consistent with HapMap data for the CHB and JPT populations, as well as with the results of a previous study (He et al., 2011) in Japanese Americans. These results indicate a possible monomorphy and unnecessary redundancy for further assessment of rs16892766 in Asian populations.

In conclusion, this association study investigated 12 newly identified SNPs from CRC GWAS as genetic susceptibility factors for GC in a Chinese population. The present replication of genetic associations from CRC to GC highlights the utility of case-control follow-up studies to confirm novel associations characterized in large GWAS of digestive system dis-

eases. Our study provides the first reported data of a possible association between the SNPs rs4444235 and rs10411210 and GC risk. These SNPs require further investigation before definitive conclusions can be drawn.

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Supplementary material

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