Original Article

Variant *TP53BP1* rs560191 G>C is associated with risk of gastric cardia adenocarcinoma in a Chinese Han population

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Objective: To investigate the association between gastric cardia adenocarcinoma (GCA) and ten functional single nucleotide polymorphisms (SNPs), including *TP53BP1* rs560191 G>C, *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A, and six *C1orf10/CRNN* variants. We performed a hospital-based case-control study to evaluate the genetic effects of these SNPs.

Methods: Two hundred and forty-three GCA cases and 476 controls were enrolled in this study. A custom-by-design 48-Plex SNPscan™ Kit was used to determine their genotypes.

Results: When the *TP53BP1* rs560191 GG homozygote genotype was used as the reference group, the GC genotype was associated with a significantly increased risk of GCA. The CC genotype was not associated with the risk of GCA compared with the GG genotype. None of the *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A or the six *C1orf10/CRNN* polymorphisms showed a significant difference in genotype distributions between the cases and the controls.

Conclusions: The results demonstrated that the functional polymorphism *TP53BP1* rs560191 G>C might contribute to GCA susceptibility. However, the statistical power of our study was limited. Large, well-designed studies and further functional investigations are needed to confirm our findings.

Keywords: *TP53BP1*; polymorphisms; gastric cardia adenocarcinoma (GCA); molecular epidemiology

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Introduction

Gastric cardia adenocarcinoma (GCA) is one of the most common malignant tumors and is among the leading causes of cancer-related death. GCA has increased dramatically in North America and Western European countries (1). In China, GCA shares very similar geographic distribution with esophageal squamous cell carcinoma (ESCC) epidemiologically (1,2). Both genetic and environmental factors may contribute to the etiology of GCA (3). Single nucleotide polymorphisms (SNPs), accounting for >90% of genetic variations, may influence the function of genes (4). SNPs have been suggested to affect individual differences in disease susceptibility (5).

Apoptosis is a crucial mechanism against hyper-proliferation and malignancy, and has been considered as a fundamental component in cancer pathogenesis (6). *Caspase8* (*CASP8*), *Caspase7* (*CASP7*), tumor protein 53-binding protein 1 (*TP53BP1*) and *C1orf10/Cornulin* (*CRNN*) are among key genes related to apoptosis. CASP8 is an initiator CASP and a key regulator of apoptosis, which plays an important role in cancer development and progression (7). In critical cell structures, CASP7 conducts a coordinated program of proteolysis and resulting in destruction, acting as an executioner CASP (8). TP53BP1 interacts specifically with *p53* and helps mediate the DNA damage checkpoint (9). TP53BP1 participates in both

DNA repair and cell cycle control. TP53BP1 contains two BRCA1 C-terminal (BRCT) domains, which are essential for its tumor suppressor functions (10). Available functional data also suggests that the C1orf10/CRNN protein might protect against apoptosis during cellular responses to stress (11).

In a previous study, we investigated the associations between functional polymorphisms *TP53BP1* rs560191 G>C, *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* variants and ESCC susceptibility in a hospital-based case-control study (12). In this study, we hypothesize that these SNPs may alter individual risk of GCA. Thus, we performed genotyping analyses for the 10 SNPs using 243 GCA cases and 476 controls in a Chinese Han population.

Patients and methods

Ethical approval of study protocol

The Review Board of Jiangsu University (Zhenjiang, China) approved this study (Zhenjiang, China). All subjects included in the study gave written informed consent. We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

Study subjects

From October 2008 to July 2010, 243 GCA patients contained in the case group were consecutively recruited at the Affiliated People's Hospital of Jiangsu University and Affiliated Hospital of Jiangsu University (Zhenjiang, China). For all the cases, pathological examination was used to make a definite diagnosis. Tumor, nodal, and metastatic (TNM) stage was according to the seventh edition of the Union for International Cancer Control (UICC) TNM staging (13). The exclusion criteria included: patients who previously had cancer or any metastatic cancer, received radiotherapy or chemotherapy. A total of 476 cancer-free controls were contained in this study, and among which 380 controls were recruited from the two hospitals aforementioned during the same time period. Another 96 controls were recruited from hospitals in Changzhou city (which is adjacent to Zhenjiang) as previous described (14). The controls were matched to the cases in terms of age (±5 years) and sex. Most of the controls were admitted to the hospitals to receive treatment for trauma.

Using a pre-tested questionnaire, each patient was personally questioned by trained investigator to obtain information on demographic data (e.g., age, sex) and related environmental risk factors (including tobacco using and alcohol consumption). Individuals who smoked one cigarette per day for >1 year were considered to be "smokers". Subjects who consumed ≥3 alcoholic drinks a week for >6 months were defined as "alcohol drinkers". After the investigation, 2 mL venous blood sample was collected from each subject.

DNA extraction and genotyping analysis

Blood samples were collected from subjects using Vacutainers and drawn into tubes lined with ethylenediamine tetra-acetic acid (EDTA). The QIAamp DNA Blood Mini Kit (Qiagen, Berlin, Germany) was used to extract genomic DNA from peripheral blood (15). Sample DNA (10 ng) was amplified by PCR according to the manufacturer's recommendations. A custom-by-design 48-Plex SNPscan™ Kit (Genesky Biotechnologies Inc., Shanghai, China) was used to determine genotypes of the ten SNPs as previously described (1,16-18). This kit was developed according to patented SNP genotyping technology by Genesky Biotechnologies Inc., which was substantially based on double ligation and multiplex fluorescence PCR. Repeated analyses were accomplished to guarantee the genotyping quality by randomly choosing 4% of samples with high DNA quality.

Statistical analysis

Differences in the distributions of demographic characteristics, selected variables, and genotypes of the *TP53BP1* rs560191 G>C, *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* variants between the cases and controls were estimated using the χ^2 test. The associations between the ten SNPs and susceptibility of GCA were evaluated by calculating the odds ratios (ORs) and their 95% confidential intervals (95% CIs) using logistic regression analyses for crude ORs and adjusted ORs when 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 the expected ones among the control group. All statistical analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

Table 1 Distribution of selected demographic variables and risk factors in GCA cases and controls

Variable	Cases (n=243)		Controls (n=476)		P*
	n	%	n	%	
Age (year, $\bar{x}\pm s$)	64.90±8.65		64.76±7.46		0.832
<65	126	51.9	245	51.5	0.923
≥65	117	48.1	231	48.5	
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	
Lymph node metastasis					
LN meta (+)	122	55.5			
LN meta (–)	98	44.5			
TNM stages					
I	24	12.2			
II	34	17.3			
III	101	51.5			
IV	37	18.9			

*, two-sided χ^2 test and student *t*-test; LN information was available in 220 GCA cases. TNM information was available in 196 GCA cases. LN meta, lymph node metastasis. Abbreviations: GCA, gastric cardia adenocarcinoma; TNM, tumor, nodal, and metastatic stage.

Results

Characteristics of study population

Characteristics of cases and controls included in the study are summarized in *Table 1*. The cases and controls appeared to be adequately matched on age and sex as suggested by the χ^2 tests (P=0.923 and P=0.197, respectively). As shown in *Table 1*, no significant difference was detected on drinking status between the cases and the controls (P=0.217), but smoking rate was higher in GCA patients than in control subjects (P=0.004). Lymph node metastasis information was available in 220 (90.5%) of 243 GCA patients; regional lymph node metastasis was present in 122 (55.5%) cases. TNM stage data were available in 196 (80.7%) of 243 patients (stage I: 24; stage II: 34; stage III: 101, stage IV: 37). The primary information for ten genotyped SNPs is shown in *Table 2*. For the ten SNPs, the genotyping was successful ranging from 97.06% to 97.90% in all 719 samples. The concordance rates of repeated analyses were 100%. Minor allele frequency (MAF) in our controls was similar to MAF for Chinese in database for all ten SNPs. The observed genotype frequencies for these ten polymorphisms in the controls were in HWE except *TP53BP1* rs560191 G>C (*Table 2*).

Associations between ten polymorphisms and risk of GCA

The genotype distributions of *TP53BP1* rs560191 G>C, *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* in the cases and the controls are shown in *Table 3*. In the single locus analyses, the genotype frequencies of *TP53BP1* rs560191 G>C were 31.17% (GG), 55.41% (GC), 13.42% (CC) in the case patients and 37.07% (GG), 41.59% (GC), 21.34% (CC) in the control subjects, and the difference was statistically significant (P=0.001). When the *TP53BP1* rs560191 GG homozygote genotype was used as the reference group, the GC genotype

Table 2 Primary information for ten genotyped SNPs

Genotyped SNPs	Chr	Regulome DB Score*	Location	MAF for Chinese in database	MAF in our controls (n=476)	P for HWE test in controls	Genotyping value (%)
TP53BP1: rs560191 G>C	15	4	nonsynon_exon 9	0.444	0.421	<0.05	97.48
CASP8: rs1035142 G>T	2	1f	3'-Flanking	0.271	0.294	0.646	97.27
CASP7: rs3127075 G>C	10	2a	Intron 2	0.140	0.174	0.721	97.69
CASP7: rs7907519 C>A	10	2b	5'-UTR_intron 1	0.289	0.280	0.415	97.90
C1orf10/CRNN: rs3753443 C>T	1	No Data	5'-Flanking	0.476	0.436	0.833	97.06
C1orf10/CRNN: rs3753444 C>G	1	6	5'-Flanking	0.456	0.438	0.896	97.90
C1orf10/CRNN: rs3753446 C>A	1	No Data	5'-Flanking	0.467	0.457	0.693	97.69
C1orf10/CRNN: rs3829868 C>T	1	No Data	nonsynon_exon 3	0.476	0.438	0.896	97.90
C1orf10/CRNN: rs4285700 C>A	1	6	5'-Flanking	0.476	0.438	0.896	97.90
C1orf10/CRNN: rs10888486 C>T	1	No Data	3'-UTR_exon 3	0.476	0.438	0.896	97.90

*, http://www.regulomedb.org. Abbreviations: Chr, chromosome; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; UTR, untranslated region.

Table 3 Main effects of SNPs on GCA risk

Genotyped SNPs	Genotyping		AB *vs*. AA Adjusted OR* (95% CI); P	BB vs. AA Adjusted OR* (95% CI); P	P trend
	Case (n=243) (AA/AB/BB)	Control (n=476) (AA/AB/BB)			
TP53BP1: rs560191 G>C	72/128/31	172/193/99	1.58 (1.11-2.26); 0.012	0.74 (0.45-1.21); 0.235	0.001
CASP8: rs1035142 G>T	108/109/16	233/188/42	1.25 (0.89-1.77); 0.200	0.76 (0.39-1.49); 0.424	0.248
CASP7: rs3127075 G>C	168/58/6	316/136/13	0.83 (0.58-1.19); 0.306	0.93 (0.34-2.53); 0.891	0.479
CASP7: rs7907519 C>A	123/101/11	238/195/33	0.99 (0.72-1.38); 0.971	0.66 (0.32-1.36); 0.262	0.465
C1orf10/CRNN: rs3753443 C>T	69/105/43	148/225/89	1.03 (0.71-1.49); 0.880	1.08 (0.67-1.72); 0.755	0.986
C1orf10/CRNN: rs3753444 C>G	69/119/47	148/228/90	1.15 (0.80-1.66); 0.444	1.15 (0.73-1.82); 0.552	0.810
C1orf10/CRNN: rs3753446 C>A	64/112/52	135/235/95	1.05 (0.72-1.53); 0.804	1.18 (0.75-1.86); 0.482	0.772
C1orf10/CRNN: rs3829868 C>T	70/119/46	148/228/90	1.14 (0.79-1.64); 0.493	1.12 (0.70-1.77); 0.645	0.864
C1orf10/CRNN: rs4285700 C>A	69/120/46	148/228/90	1.16 (0.81-1.67); 0.422	1.13 (0.71-1.80); 0.604	0.803
C1orf10/CRNN: rs10888486 C>T	70/119/45	148/228/89	1.14 (0.79-1.64); 0.490	1.09 (0.68-1.73); 0.725	0.866

*, adjusted for age, sex, smoking and drinking status; AA/AB/BB means homozygote, heterozygote and mutated homozygote.

Table 4 Stratified analyses between *TP53BP1* rs560191 G>C polymorphism and GCA risk by sex, age, smoking status and alcohol consumption

Variable	*TP53BP1*: rs560191 G>C (case/control)*				Adjusted OR** (95% CI); P			
	GG	GC	CC	GC+CC	GG	GC	CC	GC+CC
Sex								
Male	51/108	77/117	21/58	98/175	1.00	1.36 (0.87-2.12); P: 0.179; P_h: 0.316	0.74 (0.40-1.36); P: 0.330; P_h: 0.953	1.15 (0.76-1.76); P: 0.507; P_h: 0.422
Female	21/64	51/76	10/41	61/117	1.00	1.92 (1.03-3.58); P: 0.039; P_h: 0.316	0.75 (0.31-1.78); P: 0.507; P_h: 0.953	1.52 (0.84-2.76); P: 0.167; P_h: 0.422
Age								
<65 year	40/94	65/104	18/39	83/143	1.00	1.40 (0.85-2.29); P: 0.184; P_h: 0.657	1.02 (0.52-2.03); P: 0.950; P_h: 0.154	1.29 (0.81-2.07); P: 0.280; P_h: 0.788
≥65 year	32/78	63/89	13/60	76/149	1.00	1.71 (1.01-2.90); P: 0.046; P_h: 0.657	0.54 (0.26-1.11); P: 0.095; P_h: 0.154	1.24 (0.75-2.05); P: 0.393; P_h: 0.788
Smoking status								
Never	47/116	76/140	15/69	91/209	1.00	1.34 (0.86-2.09); P: 0.200; P_h: 0.195	0.47 (0.24-0.93); P: 0.029; P_h: 0.120	1.05 (0.69-1.61); P: 0.826; P_h: 0.138
Ever	25/56	52/53	16/30	68/83	1.00	2.13 (1.13-4.01); P: 0.019; P_h: 0.195	1.19 (0.53-2.64); P: 0.676; P_h: 0.120	1.79 (0.99-3.24); P: 0.054; P_h: 0.138
Alcohol consumption								
Never	51/123	91/145	18/71	109/216	1.00	1.49 (0.97-2.29); P: 0.072; P_h: 0.668	0.56 (0.30-1.06); P: 0.074; P_h: 0.278	1.18 (0.78-1.78); P: 0.430; P_h: 0.539
Ever	21/49	37/48	13/28	50/76	1.00	1.78 (0.89-3.54); P: 0.101; P_h: 0.668	1.00 (0.42-2.38); P: 0.995; P_h: 0.278	1.49 (0.78-2.83); P: 0.225; P_h: 0.539

*, the genotyping was successful in 231 (95.1%) GCA cases, and 464 (97.5%) controls for *TP53BP1* rs560191 G>C; **, adjusted for age, sex, smoking status and alcohol consumption (besides stratified factors accordingly) in a logistic regression model; Ph, P for heterogeneity; Bonferroni correction was performed to correct the P value; $P_{correct}$ >0.05 in all comparison models.

was associated with a significantly increased risk for GCA (GC *vs.* GG: adjusted OR =1.58, 95% CI =1.11-2.26, P=0.012). The CC genotype was not associated with the risk of GCA compared with the GG genotype (CC *vs.* GG: adjusted OR =0.74, 95% CI =0.45-1.21, P=0.235) (*Table 3*).

None of the *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* polymorphisms achieved a significant difference in the genotype distributions between the cases and the controls. Logistic regression analyses revealed that these nine polymorphisms were not associated with the risk of GCA (*Table 3*). Bonferroni correction was performed to correct the P value; $P_{correct}$>0.05 in all comparison models for the ten polymorphisms (*Table 3*).

Stratification analyses of TP53BP1 rs560191 G>C polymorphism and risk of GCA

To evaluate the effects of *TP53BP1* rs560191 G>C genotypes on GCA risk according to different age, sex, smoking and alcohol drinking status; we performed the stratification analyses. A significantly increased risk of GCA associated with the *TP53BP1* rs560191 G>C polymorphism was evident among female patients, older patients and patients who smoked. A significantly decreased risk of GCA associated with the *TP53BP1* rs560191 G>C polymorphism was evident among patients who never smoked (*Table 4*). Bonferroni correction was performed to correct the P value; $P_{correct}$>0.05 in all comparison models (*Table 4*).

Discussion

We conducted this study to investigate the associations of *TP53BP1* rs560191 G>C, *CASP8* rs1035142 G>T, *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* SNPs with susceptibility to GCA in a high risk Chinese population. Our findings revealed that the variant

TP53BP1 rs560191 GC genotype was associated with a significantly increased risk of GCA.

TP53BP1 interacts specifically with *p53*, which was a well known tumor-associated gene (19). TP53BP1 binds to *p53* and plays a role in responses to DNA damage. A study in Japan revealed that *TP53BP1* rs560191 G>C and *p53* Arg72Pro polymorphism had significant interaction in lung cancer risk (20). By cooperating with damage sensors and signal transducers, TP53BP1 helps mediate the DNA damage checkpoint (9). TP53BP1 plays an important role in both DNA repair and cell cycle control (21). TP53BP1 contains two BRCT domains, which are essential for tumor suppressor functions (10). *TP53BP1* SNPs may play an important role in the etiology of cancer because of the direct role of TP53BP1 in the cellular response to DNA damage. Previous studies revealed no association between *TP53BP1* rs560191 G>C (Asp353Glu) SNPs and cancer risk (22-27); however, Kiyohara reported that the *TP53BP1* rs560191 G>C SNP was associated with a decreased risk of lung cancer (20). In previous a meta-analysis, no significant association between *TP53BP1* rs560191 G>C SNP and cancer risk was found in the overall population (28).

The negative results for an association of *TP53BP1* rs560191 G>C SNP and cancer risk in these previous case-control reports and meta-analyses are not in accordance with our results. However, our stratified analysis revealed that the increased risk was largely attributed to female patients, older patients and patients who smoked. Among patients who never smoked, the SNP was protective, indicating age, sex and environment differences might play an important role in cancer etiology related to the *TP53BP1* rs560191 G>C SNP. Previously, it was found that neither *TP53BP1* rs560191 G>C polymorphism nor *CASP7* rs3127075 G>C, *CASP7* rs7907519 C>A and six *C1orf10/CRNN* are associated with the risk of ESCC, which is in accordance with our results.

The frequencies of genetic polymorphisms often vary between ethnic groups. In the current study involving Chinese subjects, the allele frequency of *TP53BP1* rs560191 C was 0.421 among 476 control subjects, which is consistent with the Chinese Han population (0.444), but lower than Sub-Saharan African population (1.000) and higher than the European population (0.308), according to the SNP DataBase (http://hapmap.ncbi.nlm.nih.gov/).

Using Power and Sample Size Calculation (PS, version 3.0, 2009, http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize), and considering *TP53BP1* rs560191 G>C mutant alleles in the control group, OR, GCA samples and control sample sizes, the power of our analysis (α=0.05) was 0.809 in the 231 GCA cases and 464 controls with an OR =1.58 for *TP53BP1* rs560191 G>C.

This study has some limitations. First, the subjects may not be representative because our study was based on hospital attendees instead of the general population. False positive results may be obtained because of inherited biases. Second, the statistical power of our study was limited because of the moderate sample size and lack of a validation cohort. Some significant findings may have occurred by chance. Third, single SNP locus analyses may not provide a comprehensive understanding of the genetic effects of these candidate genes; further fine-mapping analysis of the susceptibility region is warranted. Combinations of certain genotypes may be also more discriminating as risk factors than single locus genotypes. Finally, because of the lack of detailed information on cancer metastasis and survival, further analyses on the role of *TP53BP1* polymorphisms in GCA progression and prognosis cannot be achieved.

Conclusions

We found an association between genetic variant *TP53BP1* rs560191 G>C and susceptibility to GCA. However, the sample size is not large enough to draw precise conclusions. Further well-designed studies using a large validation set are needed to support our findings.

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