

## Association between *ITGA2* C807T polymorphism and gastric cancer risk

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### Abstract

**AIM:** To evaluate the impact of the *ITGA2* gene polymorphism on gastric cancer risk.

**METHODS:** A hospital-based case-control study was conducted, including 307 gastric cancer patients and 307 age- and gender-matched control subjects. The genotypes were identified by polymerase chain reaction-restriction fragment length polymorphism assay.

**RESULTS:** The frequencies of the wild and variant genotypes in cases were significantly different from those of controls ( $P = 0.019$ ). Compared with individuals with

the wild genotype CC, subjects with the variant genotypes (CT + TT) had a significantly higher risk of gastric cancer (adjusted odds ratio = 1.57, 95% CI = 1.13-2.17,  $P = 0.007$ ). In stratified analyses, the elevated gastric cancer risk was especially evident in older individuals aged > 58 years, nonsmokers and rural subjects. Further analyses revealed that the variant genotypes were associated with poor tumor differentiation and adjacent organ invasion in the sub-analysis of gastric cancer patients.

**CONCLUSION:** The *ITGA2* gene C807T polymorphism may be associated with an increased risk of gastric cancer, differentiation and invasion of gastric cancer.

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**Key words:** Gastric cancer; Integrin; *ITGA2*; Polymorphism; Genotype

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### INTRODUCTION

Gastric cancer remains a major public health issue as the fourth most common cancer type and the second leading cause of cancer death worldwide<sup>[1,2]</sup>. Nearly half of the gastric cancer cases occur in China<sup>[3]</sup>. Although the

cause of gastric cancer is largely unknown, it has been shown that diet, tobacco smoking, alcohol, gastroesophageal reflux and *Helicobacter pylori* (*H. pylori*) infection are associated with the risk of this cancer<sup>[4-7]</sup>. As genetic polymorphisms are responsible for the inter-individual variation and diversity, they have been recently considered as the main genetic elements involved in the development of common and complex diseases, including various cancers. Like many malignancies, it is believed that gastric cancer is the result of interactions between environmental factors and genetic factors<sup>[8]</sup>. Our previous epidemiological studies also provided the evidence that genetic polymorphisms were associated with the risk of gastric cancer<sup>[9-12]</sup>.

Integrins are members of a family of cell-surface heterodimeric proteins that mediate cell-matrix and cell-cell interactions. The 18  $\alpha$ -subunits and 8  $\beta$ -subunits form together at least 25 different integrins, each pair being specific for a unique set of ligands. It has been demonstrated that integrins may play a crucial role in carcinogenesis, tumor behavior and metastasis<sup>[13,14]</sup>. Several integrins such as  $\alpha 2\beta 1$ ,  $\alpha IIb\beta 3$  and  $\alpha v\beta 3$  are considered as key factors for cancer development and progression. Integrin  $\alpha 2\beta 1$ , also known as platelet glycoprotein I a-II a, is expressed by epithelial cells, and its level of expression in tumor cells is associated with motility, invasiveness and cellular differentiation<sup>[15-17]</sup>. Several studies have shown that integrin  $\alpha 2\beta 1$  expression is closely associated with invasion and metastasis of gastric cancer<sup>[18-21]</sup>.

The integrin,  $\alpha 2$  gene (*ITGA2*) is located on chromosome 5q23-31. A silent change in the coding region at nucleotide 807 (TTT/TTC at codon Phe253) has been identified. The C807T single nucleotide polymorphism (NCBI SNP ID: rs1126643) of the *ITGA2* gene was associated with the integrin  $\alpha 2\beta 1$  density. The genotype 807 TT was associated with a higher receptor density and the genotype 807 CC with a lower density, whereas heterozygous individuals expressed intermediate receptor levels<sup>[22,23]</sup>.

Recent studies indicated that the *ITGA2* gene C807T polymorphism was associated with various diseases, including stroke, retinal vein occlusion, acute coronary syndrome, colorectal cancer, and breast cancer<sup>[24-29]</sup>. To the best of our knowledge, there has been no study that assessed the association between the polymorphism and gastric cancer risk.

Given that the roles of *ITGA2* in the progression of gastric cancer as well as the effect of the polymorphism in *ITGA2* gene on the receptor function, it is plausible that the polymorphism may be associated with the risk of gastric cancer. To test the hypothesis, we performed a hospital-based case-control study in a Chinese population.

## MATERIALS AND METHODS

### Subjects

This hospital-based case-control study consisted of 307 consecutive inpatients with histologically confirmed gas-

tric cancers without synchronous and/or metachronous secondary malignancy and a population-based and sex- and age-matched 307 cancer-free inpatients as controls. All subjects were recruited between March 2005 and November 2009 from the patients who were admitted to the First Affiliated Hospital of Nanjing Medical University. The most common causes for hospitalization in the control subjects were hernias, appendicitis, hydrocele, cholecystitis and cataract. All subjects were of unrelated Han nationality from Jiangsu Province or its surrounding regions. Information on age, gender, smoking status, residence (urban or rural), body weight and personal medical history was collected by questionnaire. Individuals who formerly or currently smoked  $\geq 10$  cigarettes per day for at least 2 years were defined as smokers. Depth of tumor invasion and local lymph node status were classified according to the TNM classification criteria of International Union Against Cancer<sup>[30]</sup>. Differentiation was graded according to World Health Organization classification. The study was approved by the Ethics Committee of Nanjing Medical University First Affiliated Hospital and informed consent was obtained from all the participating subjects.

### Genotyping

The protocol for genomic DNA extraction was described in our previous study<sup>[9]</sup>. The polymerase chain reaction (PCR)-restriction fragment length polymorphism assay was used to identify the *ITGA2* C807T genotypes. The PCR was performed in a total volume of 20  $\mu$ L reaction mixtures containing 2  $\mu$ L 10  $\times$  PCR buffer (MBI Fermentas), 1.75 mmol/L  $MgCl_2$ , 0.25  $\mu$ mol/L each primer (forward 5'-GTGTTTAACCTGAACACATAT-3', reverse 5'-ACCTTGCATATTGAATTGCTT-3'), 0.15 mmol/L dNTP, 1 unit *Taq* polymerase (MBI fermentas) and 150 ng genomic DNA. The amplification protocol is as follows: primary denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s, and extension at 72°C for 1 min, then a final elongation at 72°C for 5 min. The 115 bp PCR products including the polymorphic site were digested at 65°C for 12 h, using restriction enzyme *Taq* I (MBI Fermentas) and then separated on a 3% ethidium bromide-stained agarose gel. The wild-type homozygotes (CC) produced two bands at 92 and 23 bp, while the variant homozygotes (TT) produced one band at 115 bp, and the heterozygous (CT) produced three bands at 115, 92 and 23 bp (Figure 1). To control the quality of genotyping, all assays were conducted by two researchers separately in a blind fashion. In addition, a 10% masked samples were randomly selected and retested, and the reproducibility was 100%.

### Statistical analysis

Statistical analyses were conducted using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed and  $P < 0.05$  was considered statistically significant. Quantitative variables departing from the normal distribution including age and weight were summarized as median and analyzed by Mann-Whitney rank

Table 1 Demographic information *n* (%)

Characteristics	Cases ( <i>n</i> = 307)	Controls ( <i>n</i> = 307)	<i>P</i> value
Gender (male)	231 (75.2)	231 (75.2)	1.000
Age <sup>1</sup> (yr), (range)	59 (50-68)	58 (49-66)	0.145
Weight <sup>1</sup> (kg), (range)	62 (55-70)	65 (57-72.75)	0.001
Hypertension	65 (21.17)	59 (19.22)	0.546
Diabetes	17 (5.54)	24 (7.82)	0.262
Smoking	82 (26.71)	53 (17.26)	0.005
Residence			
Rural	139 (45.28)	139 (45.28)	1.000
Urban	168 (54.72)	168 (54.72)	

<sup>1</sup>Median (25th-75th percentiles).

sum test. Pearson's  $\chi^2$  test was used to compare the difference in the distribution of categorical variables and genotype frequencies between cases and controls. The Hardy-Weinberg equilibrium of the *ITGA2* genotypes was estimated for cases and controls by a goodness-of-fit  $\chi^2$  test. Odds ratio (OR) and 95% CI were calculated to evaluate the association between the polymorphism and the risk of gastric cancer. Carriers of the wild genotype CC were used as the reference. The crude OR was obtained using the Woolf approximation method and the adjusted OR was calculated by unconditional logistic regression method, with adjustment for age, sex, smoking status, residence, hypertension and diabetes.

## RESULTS

### Demographic information

A total of 614 subjects (307 cases and 307 controls) were analyzed. Baseline demographic characteristics of the study groups are shown in Table 1. The age distribution and proportion of males were quite similar due to the fact that we selected the age- and gender-matched subjects. The two groups were similar with respect to residence, history of hypertension and diabetes. Nevertheless, compared with controls, gastric cancer patients had a lower body-weight ( $P = 0.001$ ) and more smokers were found among gastric cancer cases than among the controls (26.71% *vs* 17.26%,  $P = 0.005$ ).

### Distribution of *ITGA2* genotype in cases and controls and risk estimates

Table 2 shows the frequency distributions of the genotypes and their association with gastric cancer risk by unadjusted OR, adjusted OR and 95% CI. The genotype distributions in cases and controls were consistent with those from the Hardy-Weinberg equilibrium model ( $P = 0.988$ ,  $P = 0.675$ , respectively). The frequencies of the *ITGA2* genotype were significantly different between gastric cancer cases and controls ( $P = 0.019$ ). Compared with the control group, T allele frequency was significantly higher in the case group ( $P = 0.024$ ). With the wild genotype CC as reference, we found that the CT genotype was associated with an increased risk of gastric cancer (adjusted OR = 1.54, 95% CI = 1.10-2.18,  $P = 0.013$ ).

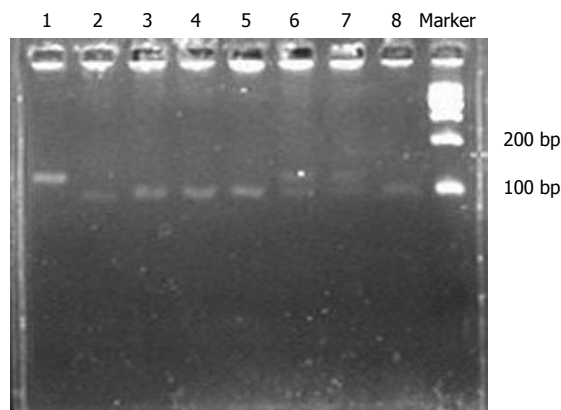


Figure 1 *ITGA2* C807T polymorphism in gastric cancer patients and controls. Amplified polymerase chain reaction products were digested with restriction enzyme *Taq* I and analyzed on a 3% agarose gel. Lane 1: The TT homozygous; Lanes 2-5: The CC homozygous; Lanes 6, 7: The CT heterozygous.

Individuals with the variant genotypes (CT + TT) had a 1.57-fold increased risk of developing gastric cancer (adjusted OR = 1.57, 95% CI = 1.13-2.17,  $P = 0.007$ ).

### Stratified analysis of polymorphism and gastric cancer risk

As shown in Table 3, stratified analyses were performed by the median age of controls (58 years), sex, smoking status, and residence. The elevated risk of gastric cancer associated with the variant genotypes was noteworthy in subjects aged > 58 years (adjusted OR = 1.88, 95% CI = 1.17-3.03,  $P = 0.010$ ), but not in subjects aged ≤ 58 years. In non-smoking subjects, the variant genotypes were associated with a 51% increased risk of gastric cancer (adjusted OR = 1.51, 95% CI = 1.05-2.18,  $P = 0.028$ ), whereas the correlation was not statistically significant in smoking subjects. When stratified by residence, the elevated risk was evident in rural subjects (adjusted OR = 2.35, 95% CI = 1.42-3.90,  $P = 0.001$ ), but not in urban subjects. No statistically significant difference was observed in the association of the polymorphism and susceptibility to gastric cancer between males and females.

### Variant genotypes and clinicopathological characteristics of gastric cancer

We also observed the correlations between the *ITGA2* variant genotypes and clinicopathologic features of gastric cancer patients in this study (Table 4). A significantly increased risk was found in individuals with the variant genotypes in both poorly differentiated tumors (adjusted OR = 2.21, 95% CI = 1.12-4.38,  $P = 0.022$ ) and adjacent invaded organs (adjusted OR = 2.12, 95% CI = 1.10-4.07,  $P = 0.024$ ) of gastric cancer. However, no significant association was observed between the polymorphism and lymph node metastasis or tumor location.

## DISCUSSION

In the present study, we investigated the role of *ITGA2* gene C807T polymorphism in gastric cancer susceptibility.

**Table 2** Distributions of *ITGA2* genotype in cases and controls and risk estimates *n* (%)

<i>ITGA2</i> genotype	Cases <sup>1</sup>	Controls <sup>1</sup>	Crude OR (95% CI)	<i>P</i> value	Adjusted OR <sup>2</sup> (95% CI)	<i>P</i> value
Overall	307	307				
CC	141 (45.93)	170 (55.37)	1.00		1.00	
CT	135 (43.97)	113 (36.81)	1.44 (1.03-2.01)	0.033	1.54 (1.10-2.18)	0.013
TT	31 (10.10)	24 (7.82)	1.56 (0.87-2.78)	0.133	1.62 (0.90-2.91)	0.112
CT + TT	166 (54.07)	137 (44.63)	1.46 (1.06-2.01)	0.019	1.57 (1.13-2.17)	0.007
C allele	417 (67.92)	453 (73.78)				
T allele	197 (32.08)	161 (26.22)				

<sup>1</sup>Distributions of the *ITGA2* genotype in cases and controls were in Hardy-Weinberg equilibrium ( $P = 0.988$ ,  $P = 0.675$ , respectively); <sup>2</sup>Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

**Table 3** Stratified analyses for variant *ITGA2* genotypes in cases and controls *n* (%)

Variable	(CT + TT)/CC		Crude OR (95% CI)	<i>P</i> value	Adjusted OR <sup>1</sup> (95% CI)	<i>P</i> value
	Cases	Controls				
Age (yr), (median)						
≤ 58	81 (26.4)/68 (22.1)	80 (26)/85 (27.7)	1.27 (0.81-1.97)	0.298	1.31 (0.83-2.06)	0.247
> 58	85 (27.7)/73 (23.8)	57 (18.6)/85 (27.7)	1.74 (1.10-2.75)	0.018	1.88 (1.17-3.03)	0.010
Sex						
Females	45 (14.7)/31 (10.1)	38 (12.4)/38 (12.4)	1.45 (0.76-2.76)	0.255	1.52 (0.73-2.93)	0.206
Males	110 (35.8)/121 (39.4)	99 (32.2)/132 (43)	1.21 (0.85-1.73)	0.304	1.29 (0.82-2.01)	0.287
Smoking status						
Smokers	40 (13)/42 (13.7)	19 (6.2)/34 (11.1)	1.70 (0.84-3.46)	0.141	1.87 (0.89-3.94)	0.100
Non-smokers	126 (41)/99 (32.3)	118 (38.4)/136 (44.3)	1.47 (1.02-2.10)	0.037	1.51 (1.05-2.18)	0.028
Residence						
Urban	89 (29)/79 (25.7)	84 (27.4)/84 (27.4)	1.13 (0.73-1.73)	0.585	1.17 (0.76-1.81)	0.479
Rural	77 (25.1)/62 (20.2)	53 (17.2)/86 (28)	2.02 (1.25-3.25)	0.004	2.35 (1.42-3.90)	0.001

<sup>1</sup>Adjusted for age, sex, smoking status, residence, hypertension, and diabetes. OR: Odds ratio.

**Table 4** Associations between variant *ITGA2* genotypes and clinicopathological characteristics of gastric cancer<sup>1</sup>

Variable	CT + TT	CC	Crude OR (95% CI)	<i>P</i> value	Adjusted OR <sup>2</sup> (95% CI)	<i>P</i> value
Tumor differentiation						
Well	42	42	1		1	
Moderate	65	69	0.94 (0.55-1.63)	0.830	0.94 (0.54-1.63)	0.828
Poor	55	27	2.04 (1.09-3.82)	0.027	2.21 (1.12-4.38)	0.022
Depth of tumor infiltration						
T1	24	30	1		1	
T2	21	17	1.54 (0.67-3.56)	0.308	1.76 (0.73-4.25)	0.208
T3	34	40	1.06 (0.53-2.15)	0.866	1.10 (0.52-2.32)	0.797
T4	83	51	2.03 (1.07-3.86)	0.030	2.12 (1.10-4.07)	0.024
Lymph node metastasis						
Negative	59	51	1		1	
Positive	103	87	1.02 (0.64-1.64)	0.923	0.98 (0.61-1.58)	0.942
Localization						
Cardia	38	41	1		1	
Non-cardia	128	100	1.38 (0.83-2.31)	0.217	1.38 (0.81-2.35)	0.231

<sup>1</sup>Data of seven plaintively treated cases were not obtained for the inoperable tumors; <sup>2</sup>Adjusted for age, sex, smoking status, residence, hypertension, and diabetes. OR: Odds ratio.

ity in a Chinese population. We found that the polymorphism may be associated with an increased risk of gastric cancer, differentiation and invasion of gastric cancer.

It has been reported that integrin  $\alpha 2\beta 1$  is one of the key factors accelerating tumor progression and metastasis in various types of cancers<sup>[15-21,31]</sup>. Koike *et al*<sup>[20]</sup> found that the  $\alpha 2$  integrin was expressed in the intestinal-type and

diffuse-type gastric carcinoma cells, and invasion through basement membrane and type I collagen gel was inhibited by anti- $\alpha 2$  integrin monoclonal antibody, indicating that the  $\alpha 2$  integrin plays an important role in invasion of gastric carcinoma cells. Another study conducted by Lee *et al*<sup>[32]</sup> elucidated the potential mechanisms underlying the spreading and invasiveness of gastric carcinoma



cells, the integrin transduces signaling directly *via* engagements with extracellular matrix proteins, thereby leading to the regulation of downstream intracellular signaling molecules. It also functions in collaborative (indirect) signaling, in which integrins cosignal with other membrane receptor-mediated signal pathways, e.g. growth factor receptors, G-protein coupled receptors or the transforming growth factor  $\beta$ 1 signaling pathway.

The *ITGA2* gene C807T polymorphism is associated with integrin density, but the precise molecular mechanism remains unclear. It is a silent polymorphism in codon 253 (Phe253Phe) and does not cause an altered structure of the integrin molecule, but in linkage disequilibrium with a yet unknown functional polymorphism affecting *ITGA2* expression. Another explanation could be a direct effect on the stability of the *ITGA2* mRNA, which resulted in a change of the amount of integrin protein being expressed.

Limited studies have reported the association between the polymorphism in *ITGA2* gene and cancer risks, although the results remain inconsistent<sup>[27-29]</sup>. Gerger *et al*<sup>[27]</sup> found that the *ITGA2* gene C807T polymorphism was associated with reduced colorectal cancer risk (OR = 0.77, 95% CI = 0.64-0.94,  $P = 0.011$ ). In their another case-control study, they found that carriers of the most common *ITGA2* haplotype (807C\_1648G) had a decreased risk for breast cancer (OR = 0.72, 95% CI = 0.53-0.98)<sup>[28]</sup>. Nevertheless, Ayala *et al*<sup>[29]</sup> reported that no association was observed between the *ITGA2* gene C807T polymorphism and breast cancer risk.

Based on these studies, we conducted this hospital-based case-control study to investigate the association between the *ITGA2* gene C807T polymorphism and the risk of gastric cancer in a Chinese population. The frequency of the variant T allele in our control group was 26.22%, which was similar to that in another study in a Chinese Taiwanese population (27.1%)<sup>[33]</sup> and HapMap database (26.7% for Han Chinese). Our results showed that the variant genotypes had a 57% increased risk of developing gastric cancer.

In the subgroup analyses, we found that the polymorphism was associated with the increased risk of gastric cancer in the subgroup of the subjects aged > 58 years, but not in the subjects aged  $\leq 58$  years. Milne *et al*<sup>[34]</sup> indicated that carcinogenesis is considered as accumulation of genetic events, and gastric cancer has a steep slope for age-specific increase in incidence. The increased risk observed in older subjects implies that the *ITGA2* genotype effects tend to be age specific. The polymorphism may contribute to elevated integrin  $\alpha$ 2 $\beta$ 1 levels beyond the age of 58, thus representing a significant risk factor in this age group. However, this is just a hypothesis to interpret the results of our study, and further research is warranted to clarify the mechanism underlying the interaction between the polymorphism and age.

Similarly, in statistical analyses stratified by smoking status, a significant association was observed in non-smokers, but not in smokers. Tobacco smoking has been

undoubtedly accepted as a independent risk factor for gastric cancer<sup>[3,5,6]</sup>. The association between the polymorphism and gastric cancer risk could be masked by the overwhelming accumulated exposure to tobacco carcinogens in smokers so that the association is more evident in nonsmokers.

We also noted that increased risk of gastric cancer associated with the polymorphism was pronounced in rural subjects, but not in urban subjects. It has been suggested that the genetic differences have their strongest effects under conditions of low environmental pollution<sup>[9,35]</sup>. Our results plausibly agree with the hypothesis that the genetic effects might be more prominent in the better environments of rural areas<sup>[9]</sup>. However, this result may be found accidentally, further studies are needed to verify it.

In addition, in the stratified analyses by clinicopathological characteristics of gastric cancer, we observed a significant correlation of the variant genotypes with poorly differentiated tumors. Similarly, Langsenlehner *et al*<sup>[28]</sup> suggested that a histological grade of 3 or 4 was found more often in breast cancer subjects with TT genotype. The result is consistent with our findings. In contrast, Yasoshima *et al*<sup>[21]</sup> found no correlation between the expression of integrin  $\alpha$ 2 $\beta$ 1 and histopathological features such as the histological grade, stromal type, and infiltrating growth pattern. We also observed the significant association of the variant genotypes with adjacent organ invasions. Several studies have suggested that integrin  $\alpha$ 2 $\beta$ 1 was closely associated with invasion and metastasis in gastric cancer or tumor cells<sup>[18-21,31]</sup>. These studies might explain the result we observed. However, no correlation between the polymorphism and lymph node metastasis or location of gastric cancer was found in the stratified analyses. Because the number of cases in the subgroups was relatively small and clinicopathological variables were obtained at the time of diagnosis, our findings should be interpreted with caution before being confirmed in further studies. Thus, large-sized studies which prospectively follow up the clinical outcome, especially the survival rate, may be required to elucidate the association between the polymorphism and gastric cancer progression as well as prognosis.

Some limitations may exist in the present study. First, our study is a hospital-based case-control study, so we can not rule out the selection and recall bias. Nevertheless, the T allele frequency in control subjects is quite similar to that reported in HapMap database for Han Chinese in Beijing (0.262 in our study *vs* 0.267 in HapMap database) and the genotype distributions of cases and controls were in Hardy-Weinberg equilibrium. The second limitation is our relatively small sample size, with 307 cases and 307 controls. So gene-environment interactions may have been underpowered in stratified analyses. However, our preliminary data certainly provides some interesting information and valuable guidance for the future studies in this area. Finally, no enough information on *H. pylori* status was available in cases and controls, because of the ethical reasons.

In conclusion, the present study provides evidence that the *ITGA2* gene C807T polymorphism is associated with an increased risk of gastric cancer in a Chinese population. The association is especially evident in older individuals, non-smokers and rural subjects, and the variant genotypes may also play a role in the differentiation and invasion of gastric cancer, indicating that the polymorphism may be a useful diagnostic marker for genetic susceptibility to gastric cancer. Further studies with larger samples and functional studies are needed to elucidate the role of genetic variations in *ITGA2* and the pathogenesis of gastric cancer.

## COMMENTS

### Background

Integrin  $\alpha 2 \beta 1$  has been considered as a key factor for cancer development and progression, especially in gastric cancer. Polymorphisms in *ITGA2* gene is responsible for the expression of integrin  $\alpha 2 \beta 1$ . Recent studies indicated that the *ITGA2* gene C807T polymorphism was associated with cancer risk.

### Research frontiers

Using polymerase chain reaction-restriction fragment length polymorphism method, this study explored the relationship between *ITGA2* C807T polymorphism and gastric cancer risk.

### Innovations and breakthroughs

The results suggest that the polymorphism is associated with the elevated risk of gastric cancer in a Chinese population, especially in older individuals aged > 58 years, nonsmokers, and rural subjects. Further analyses revealed that the polymorphism may play a role in differentiation and invasion of gastric cancer.

### Applications

The results of this study could help further understand the genetic determinants of gastric cancer. The polymorphism may be a useful diagnostic marker for genetic susceptibility to gastric cancer.

### Terminology

Integrins are members of a family of cell-surface heterodimeric proteins that mediate cell-matrix and cell-cell interactions. Single nucleotide polymorphisms represent a natural genetic variability at a high density in the human genome, which are responsible for the inter-individual variation and diversity. They have been recently considered as the main genetic elements involved in the development of common and complex diseases, including various cancers.

### Peer review

The current study was designed, processed and concluded well, deserving publication.

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