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## Case Control Study

# Association between *interleukin-21* gene rs907715 polymorphism and gastric precancerous lesions in a Chinese population

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## Abstract

### BACKGROUND

The single nucleotide polymorphisms of interleukin-21 (*IL-21*) gene were confirmed to be related to various diseases, but no studies have examined the possible role of *IL-21* single nucleotide polymorphisms (SNPs) (rs907715, rs2221903, and rs12508721) in gastric precancerous lesions.

### AIM

To explore the associations between SNPs of *IL-21* gene (rs907715, rs2221903, and rs12508721) and gastric precancerous lesions in a Chinese population.

### METHODS

Three SNPs of *IL-21* were genotyped using polymerase chain reaction-ligase detection reaction in 588 cases and 290 healthy controls from May 2013 to December 2016 in northwestern China. Gastric precancerous lesions were confirmed by endoscopic examination and categorized as non-atrophic gastritis, atrophic gastritis, and intestinal metaplasia. Descriptive statistic and logistic regression were used for data analyses.

### RESULTS

*IL-21* rs907715 genotype CC and C frequencies were higher in patients with gastric precancerous lesions than in the controls (OR = 1.59, 95%CI: 1.06-2.38,  $P = 0.013$ ; OR = 1.28, 95%CI: 1.01-2.22,  $P = 0.044$ , respectively) after adjusting for confounding factors. For SNP rs907715 in intestinal metaplasia patients,

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significant differences between cases and controls were observed in the frequencies of genotype CC and C (OR = 1.92, 95%CI: 1.24-2.98,  $P = 0.004$ ; OR = 1.53, 95%CI: 1.04-2.24,  $P = 0.028$ , respectively); for non-atrophic gastritis and atrophic gastritis patients, the CC and C genotypes showed no significant association with risk in all models. No association between either rs2221903 or rs12508721 and gastric precancerous lesions was found in the present study. In the haplotype analysis, the TC haplotype (rs907715 and rs12508721) and TT haplotype (rs2221903 and rs907715) were more frequent in the case group than control group ( $P < 0.05$ ).

## CONCLUSION

Our findings indicate that SNP rs907715 of *IL-21* gene is associated with gastric precancerous lesions. The TC haplotype (rs907715 and rs12508721) and TT haplotype (rs2221903 and rs907715) increased the risk of gastric precancerous lesions. If confirmed, these findings will shed light on the etiology of precancerous lesions.

**Key words:** *Interleukin-21* gene; Single nucleotide polymorphisms; rs907715; Gastric precancerous lesions; Intestinal metaplasia

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**Core tip:** This study investigated the associations between single nucleotide polymorphisms of interleukin-21 (*IL-21*) gene (rs907715, rs2221903 and rs12508721) and gastric precancerous lesions in a Chinese population. The results showed an association between *IL-21* rs907715 polymorphism and gastric precancerous lesions. *IL-21* rs907715 genotype CC and C frequencies were higher in patients with gastric precancerous lesions than in the controls. Single nucleotide polymorphism rs907715 increased in CC and C genotypes were associated with intestinal metaplasia patients when examined separately. These findings may help clarify the etiology of gastric cancer.

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## INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy worldwide, and ranks second in incidence and mortality among all malignancies in China<sup>[1,2]</sup>. GC is considered to be a multistep progression from non-atrophic gastritis (NAG), atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia, to gastric adenocarcinoma<sup>[3]</sup>. The worldwide prevalences of AG and IM were 33% and 25% respectively<sup>[4]</sup>. As the specific recognizable stages of the precancerous cascade<sup>[5]</sup>, gastric precancerous lesions can increase the risk of GC<sup>[6,7]</sup>, so clarifying the etiology of gastric precancerous lesions is of great significance in preventing the development of GC<sup>[8]</sup>. Multiple factors contribute to the occurrence and development of gastric precancerous lesions, including environmental factors, such as *Helicobacter pylori* infection<sup>[9,10]</sup>, high salt intake<sup>[11,12]</sup>, alcohol consumption<sup>[12]</sup>, and smoking status<sup>[13]</sup>. Some studies have explored genetic risk factors for precancerous lesions such as *interleukin* (*IL*)-1, *IL*-8, *IL*-10, and *IL*-22<sup>[14-18]</sup>, but less attention has been given to *IL*-21.

*IL-21* is an immune modulatory cytokine produced mainly by activated CD4<sup>+</sup>T cells and natural killer (NK) cells, and has multiple effects on innate and adaptive immune responses<sup>[19]</sup>. The activity of *IL-21* is mediated via binding to a compound receptor consisting of *IL*-21R and  $\gamma$  chain<sup>[20,21]</sup>, and the biological functions of *IL*-21 include promoting T-cell proliferation, stimulating B-cell differentiation, and enhancing NK-cell activation<sup>[22,23]</sup>. *IL*-21 plays important roles in inflammatory, antiviral, and antitumor responses<sup>[24]</sup>. Single nucleotide polymorphisms (SNPs) of the *IL*-21 gene can change the expression level of mRNA, resulting in a change in protein expression or



autoantibody production<sup>[25]</sup>. SNPs of *IL-21* have been associated with various diseases of the immune system including systemic lupus erythematosus<sup>[26]</sup>, Graves' disease<sup>[27]</sup>, rheumatoid arthritis<sup>[28]</sup>, and hepatitis B virus (HBV) infection<sup>[29]</sup>. Several SNPs of *IL-21* (rs907715, rs2221903 and rs12508721) have also been associated with the susceptibility to cancer<sup>[30-33]</sup>. For example, SNPs rs907715 and rs2221903 reduce the susceptibility to non-small cell lung cancer<sup>[30]</sup>, and SNP rs12508721 is related to thyroid cancer<sup>[31]</sup>, breast cancer<sup>[32]</sup> and HBV-related hepatocellular carcinoma<sup>[33]</sup>. Previous studies have found that *IL-21* may be associated with the risk of gastric precancerous lesions<sup>[34,35]</sup>. However, no studies have examined the possible role of *IL-21* SNPs (rs907715, rs2221903 and rs12508721) in gastric precancerous lesions. Therefore, the present study explored associations between SNPs of *IL-21* (rs907715, rs2221903 and rs12508721) and risk of gastric precancerous lesions in a northwestern Chinese population.

## MATERIALS AND METHODS

### Subjects

This study was conducted from May 2014 to December 2016 in hospitals from three cities (Yulin, North; Xi'an, Middle; Hanzhong, South) in Shaanxi Province, China (Figure 1). Men and women with gastrointestinal symptoms requiring upper endoscopy examination were screened for study eligibility. Individuals diagnosed with GC were excluded, while a total of 1674 subjects who had undergone upper gastrointestinal endoscopy, completed pathological and 24-hour urine testing were included. The medical records of all subjects were reviewed retrospectively.

Of the eligible and willing subjects, 588 with NAG, AG, or IM (cases) and 290 without any diagnosis of gastric diseases or *H. pylori* infection (controls) were enrolled. This study was performed in accordance with the Declaration of Helsinki of the World Medical Association and was approved by the Institutional Review Board of Xi'an Jiaotong University Health Science Center. Informed consent was obtained from all subjects.

### Data measurements and collection

Demographic information was obtained from subjects' medical records including age, gender, smoking status, drinking status, height, and weight. For smoking status and drinking status, subjects were dichotomized as "yes" or "no". Body mass index was calculated as weight in kilograms divided by height in meters squared.

Daily salt intake was determined by 24-hour urine sodium excretion and was dichotomized as "high salt" and "non-high salt" according to the median of the controls (representing the general population). Subjects were asked to excrete and discard their first urine at 7 a.m. and to collect all urine over the following 24-hours, including the next day first urine at 7 a.m. Total volumes of the collection were measured. Urinary sodium levels were measured by the ion selective electrode method using by Olympus AU 680 autoanalyser.

In this study, NAG, AG, and IM were diagnosed by endoscopic findings and based on updated Sydney system criteria<sup>[36]</sup> and Atrophy Club criteria<sup>[37]</sup>. The serum *H. pylori* IgG antibody test was performed by an enzyme-linked immunosorbent assay on the same day of endoscopy. IgG values  $\geq 10$  U/mL were considered as "*H. pylori* infection" and  $< 10$  U/mL as negative results<sup>[38]</sup>.

### Genotyping

Three SNPs (rs907715, rs2221903, and rs12508721) of *IL-21* were genotyped in cases and controls. Genomic DNA was extracted from 5 mL peripheral blood samples using the Blood DNA Kit (Tiangen, Beijing, China), and stored at  $-80^{\circ}\text{C}$  until subsequent assay. SNPs were genotyped using the polymerase chain reaction (PCR)-ligase detection reaction method using assay-on-demand probes and primers: C\_8949748\_10 for rs907715, C\_16167441\_10 for rs2221903, C\_1597500\_10 for rs12508721. The forward and reverse primers are shown in Table 1. All primers were designed using the Primer3 program ([http://frodo.wi.mit.edu/cgi-bin/primer3/primer3\\_www.cgi](http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi)). The reaction was performed in a total volume of 20  $\mu\text{L}$ , containing genomic DNA (1  $\mu\text{L}$ ), buffer (2  $\mu\text{L}$ ),  $\text{MgCl}_2$  (0.6  $\mu\text{L}$ ), dNTPs (2  $\mu\text{L}$ ), *Taq* polymerase (0.2  $\mu\text{L}$ ), 2  $\mu\text{L}$  of each primer, and 12.2  $\mu\text{L}$  ddH<sub>2</sub>O. PCR conditions were as follows: denaturation at  $95^{\circ}\text{C}$  for 2 min,  $94^{\circ}\text{C}$  for 30 s; annealing at  $56^{\circ}\text{C}$  for 90 s; extension at 40 cycles of  $65^{\circ}\text{C}$  for 30 s, and a final extension at  $65^{\circ}\text{C}$  for 10 min. Following amplification, PCR products were submitted for DNA sequencing.

Trizol was used for extraction of mRNA from six intestinal epithelium tissues according to the manufacturer's instructions. Quantification of mRNA of rs907715

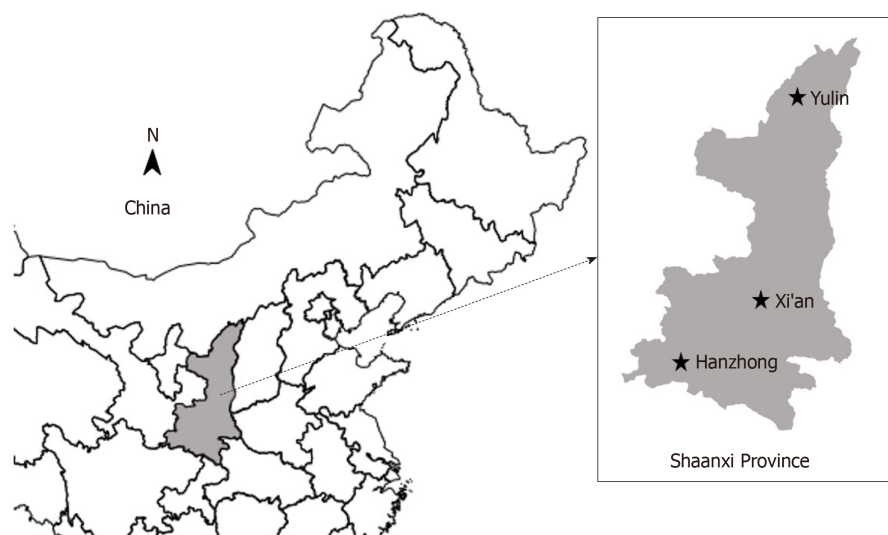


Figure 1 Location map of three selected cities in Shaanxi province, China.

was performed using BioEasy SYBR Green Real Time PCR Kit in a 20  $\mu$ L reaction volume, containing SYBR Green Master Mix (10  $\mu$ L), PCR Forward Primer (0.8  $\mu$ L), cDNA (2  $\mu$ L), ROX (0.4  $\mu$ L) and nuclease-free water (6  $\mu$ L). Extension was performed under the following conditions: Initial denaturation at 95 °C for 5 min, followed by 40 cycles at 95 °C for 5 s and 60 °C for 34 s. All reactions were performed in duplicate. Using the  $2^{-\Delta\Delta Ct}$  method<sup>[39]</sup> to calculate the relative mRNA expression levels.

### Statistical analysis

Descriptive statistics were used to describe demographic characteristics of all subjects in our study. Genotype frequencies of three SNPs (rs907715, rs2221903, and rs12508721) were obtained by statistical description, and Hardy-Weinberg equilibrium was analyzed using the chi-squared goodness of fit test. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of gastric precancerous lesions for genotype, controlling for demographic and lifestyle factors (age, gender, body mass index, drinking status, smoking status, daily salt intake and region). Distribution normality of *IL-21* mRNA expression was assessed using the Kolmogorov-Smirnov test, differences among three genotypes were measured using an independent sample Student's *t*-test. All analyses were performed with SPSS 22.0 software (IBM, Chicago, IL, United States). A two-tailed  $P < 0.05$  was considered statistically significant.

## RESULTS

### Demographic and lifestyle associations

A total of 1674 subjects were included in the study, aged 26 to 88 with a mean age of 49.8 (SD = 11.4). The incidences of NAG, AG, and IM were 6.9%, 6.3%, and 21.9%, respectively (Table 2). The NAG incidence in the south region was higher than that in other two regions, while AG and IM incidences in middle region were higher than those in other two regions.

High salt intake was associated with an increased risk of NAG (OR = 2.58, 95%CI: 1.21-4.88,  $P = 0.011$ ) (Table 3); *H. pylori* infection was correlated with decreased risk of AG (OR = 0.39, 95% CI: 0.65-0.99,  $P = 0.041$ ); and smoking was related to increased risk of NAG (OR = 2.15, 95%CI: 1.19-4.44,  $P = 0.015$ ) and IM (OR = 1.97, 95%CI: 1.40-2.58,  $P = 0.005$ ). Compared with the south region, subjects in the middle region had a lower risk of NAG (OR = 0.33, 95%CI: 0.28-0.51,  $P = 0.009$ ) and a higher risk of IM (OR = 2.95, 95%CI: 1.45-4.33,  $P = 0.007$ ); subjects in the north region had a lower risk of AG (OR = 0.33, 95%CI: 0.21-0.83,  $P = 0.010$ ).

### Association of *IL-21* gene polymorphisms and gastric precancerous lesions

The genotype distributions of each group were consistent with Hardy-Weinberg equilibrium ( $P > 0.05$ ) (Table 4). In univariate analyses, differences in the distribution frequency of rs907715 genotypes CC and C between cases and controls were statistically significant (OR = 1.77, 95%CI: 1.19-2.63,  $P = 0.005$ ; OR = 1.43, 95%CI: 1.02-



**Table 1** Probe primary information for genotyping *interleukin-21* gene polymorphisms

Primer	Type	Primer sequences, 5'→3'
rs907715	F	5'-ATAGATGAGGAAAGTGAGATC-3'
	R	5'-CTTGTCTTATTGATATATTCC-3'
rs2221903	F	5'-GGACCACATATTGCCAG ACAC-3'
	R	5'-GACACTGACGCCCATATTGAT-3'
rs12508721	F	5'-ATGGGACTAAAGT CAAGGTG-3'
	R	5'-AGATGGCTTCTAGAGTCTGG-3'

2.01,  $P = 0.039$ , respectively). Results were similar after adjusting for confounding factors (OR = 1.59, 95% CI: 1.06-2.38,  $P = 0.013$ ; OR = 1.28, 95% CI: 1.01-2.22,  $P = 0.044$ , respectively). Results were also similar for IM when examined separately (OR = 1.92, 95% CI: 1.24-2.98,  $P = 0.004$ ; OR = 1.53, 95% CI: 1.04-2.24,  $P = 0.028$ , respectively). The distribution frequencies of genotype CC and C were not statistically different between cases and controls in all models.

Analyses of rs907715 mRNA expression in intestinal epithelium tissue from six subjects with IM showed significant differences between CC genotype and TT genotype ( $P < 0.001$ ), CC genotype and CT genotype ( $P < 0.01$ ) (Figure 2). Similarly, rs907715 mRNA expression levels in six NAG tissues and six atrophic gastritis tissues were conducted. For NAG tissues, the expression level of rs907715 CC genotype was significantly different from that among the rs907715 CT genotype ( $P < 0.05$ ) and TT genotype ( $P < 0.01$ ) (Figure 3); for atrophic gastritis tissues, the expression level showed significant difference between rs907715 CC genotype and TT genotype ( $P < 0.05$ ) (Figure 4).

### Haplotype Analyses

The results showed that the TC haplotype (rs907715 and rs12508721) was significantly associated with AG and IM (OR = 3.91,  $P = 0.003$ ; OR = 2.02,  $P = 0.004$ , respectively), and it appeared to be a risk haplotype; the TT haplotype (rs2221903 and rs907715) was significantly associated with IM (OR = 1.44,  $P = 0.023$ ) and it appeared to be a risk haplotype (Table 5).

## DISCUSSION

Our results suggested that rs907715 genotypes CC and C confer increased susceptibility to IM and total gastric precancerous lesions, whereas no association was found for rs2221903 or rs12508721. Because we are not aware of any previous study that directly addressed these associations, our findings should be interpreted cautiously.

Regarding rs907715, Liu *et al.*<sup>[30]</sup>, for example, reported that genotype AA and A allele of rs907715 were associated with the decreased susceptibility to non-small cell lung cancer. Xiao *et al.*<sup>[31]</sup> revealed that the G allele of rs907715 increased the susceptibility to Graves' disease. Moreover, a case-control study found that serum *IL-21* levels in HBV patients with rs907715 genotype AA were lower than those in patients with genotype AG/GG; this genotype was independently related to sustained virological response<sup>[40]</sup>. A meta-analysis showed that the genotype distribution of *IL-21* rs907715 was significantly different between systemic lupus erythematosus patients and healthy controls in all genetic models<sup>[26]</sup>. All of these findings suggest that rs907715 of *IL-21* may to some extent exert effects on antitumor, antiviral and/or inflammatory processes. However, other studies have shown no association between rs907715 and thyroid cancer<sup>[31]</sup> and breast cancer<sup>[32]</sup>. Hence, the associations we observed in our study should be addressed in future studies.

The *IL-21* gene is located on human chromosome 4q26-27 and plays an important role in anti-tumor immunopathology<sup>[41]</sup>. Previous studies have found that *IL-21* is overexpressed in *H. pylori*-infected gastric mucosa<sup>[42]</sup>, and is correlated with the occurrence and development of gastritis<sup>[34,35]</sup>. Moreover, studies have found that the concentration of *IL-21* is increased in both tissue and serum of GC patients<sup>[43,44]</sup>. Thus, *IL-21* may play a role in the development and progression of GC and gastritis-related diseases. Previous evidence has shown that SNP rs907715 is associated with increased *IL-21* transcription and expression<sup>[40,45]</sup>. The rs907715, locating in the third intron of *IL-21* gene, may be a surrogate marker for mutations with functional consequences<sup>[25]</sup>. SNPs including rs907715 may be in linkage disequilibrium with a variant correlated

**Table 2** Demographic and lifestyle characteristics of participants in different regions

Characteristic	North		Middle		South		Total	
	<i>n</i> = 742	44.3 (%)	<i>n</i> = 488	29.2 (%)	<i>n</i> = 444	26.5 (%)	<i>n</i> = 1674	100 (%)
Gender								
Female	464	62.5	128	26.2	136	30.6	728	43.5
Male	278	37.5	360	73.8	308	69.4	946	56.5
BMI	742	20.0 ± 3.2	488	20.6 ± 2.8	444	20.3 ± 2.2	1674	20.6 ± 2.0
Age in yr	742	52.9 ± 15.1	488	46.3 ± 12.8	444	47.5 ± 15.0	1674	49.8 ± 11.4
< 40	110	36.2 ± 5.4	174	36.9 ± 5.2	76	36.7 ± 3.9	360	35.8 ± 2.9
40-49	220	45.1 ± 4.2	202	44.7 ± 4.5	288	44.8 ± 2.1	710	45.5 ± 2.0
50-59	150	54.6 ± 6.1	28	51.8 ± 1.9	8	54.4 ± 2.5	186	54.2 ± 2.0
≥ 60	262	66.1 ± 5.0	84	68.3 ± 11.1	72	77.0 ± 10.4	418	68.0 ± 8.4
Lifestyle								
High salt	230	31.0	112	23.0	56	12.6	398	23.8
Smoking	314	42.3	142	29.1	318	71.6	774	46.2
Drinking	286	38.5	116	23.8	184	41.4	586	35.0
Clinical diagnosis								
<i>H. pylori</i> infection	512	69.0	296	60.7	360	81.1	1168	69.8
NAG								
None	700	94.3	470	96.3	388	87.4	1558	93.1
Mild	23	3.1	10	2.1	35	7.9	68	4.1
Moderate	16	2.2	6	1.2	17	3.8	39	2.3
Severe	3	0.4	2	0.4	4	0.9	9	0.5
AG								
None	722	97.3	438	89.8	408	91.9	1568	93.7
Mild	13	1.8	33	6.8	23	5.1	69	4.1
Moderate	6	0.8	14	2.8	10	2.3	30	1.8
Severe	1	0.1	3	0.6	3	0.7	7	0.4
IM								
None	612	82.5	328	67.2	368	82.9	1308	78.1
Mild	87	11.7	104	21.3	48	10.9	239	14.3
Moderate	34	4.6	45	9.2	23	5.1	102	6.1
Severe	9	1.2	11	2.3	5	1.1	25	1.5

Data presented as (mean ± standard deviation). BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; NAG: Non-atrophic gastritis; AG: Atrophic gastritis; IM: Intestinal metaplasia.

with mRNA translation, thereafter may lead to the change of protein expression<sup>[27]</sup>. Therefore, SNP rs907715 of *IL-21* gene may alter the mRNA expression levels and regulate the function of *IL-21*. This suggested that rs907715 may be related to the risk of gastric precancerous lesions by influencing the activities of *IL-21*.

The data regarding TC haplotype frequency (rs907715 and rs12508721) in AG and IM patients compared to controls showed that this haplotype may be a risk for gastric precancerous lesions. Similarly, the TT haplotype frequency (rs2221903 and rs907715) in IM patient compared to controls showed that this haplotype may be a risk for IM. This result suggested that the two haplotypes, according to the *IL-21* polymorphisms, might be the important genetic factors for susceptibility to gastric precancerous lesions.

The present study selected subjects in three cities from north to south in Shaanxi province, which enhanced the power of population representation and made our results more credible. However, this study also has several limitations. First, all cases and controls were selected from participants experiencing upper gastrointestinal symptoms, which may cause a potential selection bias and increase the positive results of the study. Second, controls were screened from subjects with non-*H. pylori* infection and non-precancerous lesions to represent the general population, this led to a mismatched number of cases and controls, which may weaken the testing effectiveness. Third, this study was a case-control study and unable to draw a causal relationship.

**Table 3 Association between risk factors and gastric precancerous lesions**

Risk factors		NAG		AG		IM	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Age		1.09 (0.99-1.03)	0.315	0.90 (0.88-1.01)	0.412	1.01 (0.99-1.02)	0.313
BMI		1.01 (0.93-1.11)	0.421	0.89 (0.78-1.32)	0.587	1.11 (0.98-1.24)	0.134
Gender	Female	-		-		-	
	Male	1.52 (0.79-2.14)	0.156	0.91 (0.42-1.83)	0.792	1.30 (0.88-1.91)	0.199
High salt	No	-		-		-	
	Yes	2.58 (1.21-4.88)	0.011	0.59 (0.24-1.77)	0.315	1.01 (0.55-1.41)	0.699
<i>H. pylori</i> infection	No	-		-		-	
	Yes	0.59 (0.37-1.08)	0.141	0.39 (0.65-0.99)	0.041	0.90 (0.77-1.31)	0.555
Smoking	No	-		-		-	
	Yes	2.15 (1.19-4.44)	0.015	1.11 (0.77-2.10)	0.515	1.97 (1.40-2.58)	0.005
Drinking	No	-		-		-	
	Yes	1.00 (0.99-1.39)	0.057	0.731 (0.49-1.19)	0.161	0.95 (0.89-1.33)	0.668
Region	South	-		-		-	
	Middle	0.33 (0.28-0.51)	0.009	0.71 (0.46-1.99)	0.669	2.95 (1.45-4.33)	0.007
	North	0.55 (0.40-1.01)	0.053	0.33 (0.21-0.83)	0.010	1.41 (0.89-2.01)	0.313

BMI: Body mass index; *H. pylori*: *Helicobacter pylori*; NAG: Non-atrophic gastritis; AG: Atrophic gastritis; IM: Intestinal metaplasia.

In conclusion, our study found that SNP rs907715 was associated with gastric precancerous lesions, and the TC haplotype (rs907715 and rs12508721) and TT haplotype (rs2221903 and rs907715) increased the risk of gastric precancerous lesions, which may help clarify the etiology of GC. Further studies are required to elucidate the roles of rs907715 in development of gastric precancerous lesions at a molecular level, which may provide new targets for therapeutic interventions.

**Table 4** Comparison of the genotype distribution of the *IL-21* gene polymorphisms in gastric precancerous lesions

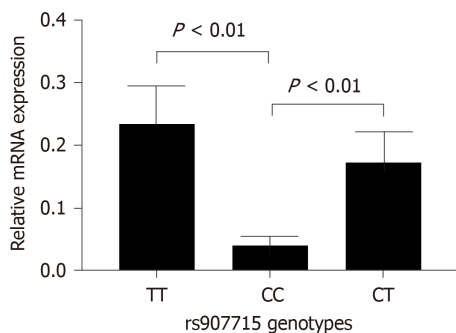
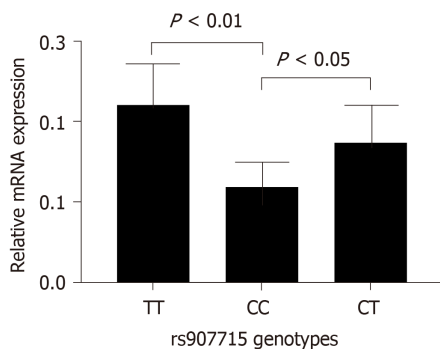
SNPs set	Geno-type	Control (n = 290, %)	NAG (n = 116, %)	AG (n = 106, %)	IM (n = 366, %)	OR <sub>1</sub>	P <sub>1</sub> value	OR <sub>2</sub>	P <sub>2</sub> value	OR <sub>3</sub>	P <sub>3</sub> value	OR <sub>4</sub>	P <sub>4</sub> value	OR <sub>5</sub>	P <sub>5</sub> value
rs907715	TT	70 (24.1)	25 (21.6)	19 (17.9)	63 (17.2)	-		-		-		-		-	
	CT	143 (49.3)	53 (45.7)	50 (47.2)	170 (46.5)	1.04 (0.60-1.81)	0.896	1.29 (0.71-2.35)	0.408	1.32 (0.88-1.98)	0.179	1.25 (0.87-1.80)	0.230	1.13 (0.62-1.74)	0.439
	CC	77 (26.6)	38 (32.7)	37 (34.9)	133 (36.3)	1.38 (0.76-2.52)	0.290	1.77 (0.93-3.36)	0.079	1.92 (1.24-2.98)	0.004	1.77 (1.19-2.63)	0.005	1.59 (1.06-2.38)	0.013
	C	220 (75.9)	91 (78.4)	87 (82.1)	303 (82.8)	1.16 (0.69-1.94)	0.578	1.46 (0.83-2.56)	0.190	1.53 (1.04-2.24)	0.028	1.43 (1.02-2.01)	0.039	1.28 (1.01-2.22)	0.044
rs12508721	TT	39 (13.4)	14 (12.1)	18 (17.0)	54 (14.8)	-		-		-		-		-	
	CT	151 (52.1)	57 (49.1)	55 (51.9)	178 (48.6)	1.05 (0.53-2.08)	0.885	0.79 (0.42-1.50)	0.467	0.85 (0.54-1.36)	0.498	0.87 (0.57-1.33)	0.525	0.82 (0.55-1.28)	0.618
	CC	100 (34.5)	45 (38.8)	33 (31.1)	134 (36.6)	1.25 (0.62-2.54)	0.529	0.72 (0.36-1.42)	0.335	0.97 (0.60-1.57)	0.895	0.96 (0.62-1.50)	0.863	0.88 (0.59-1.33)	0.879
	C	251 (86.6)	102 (87.9)	88 (83.0)	312 (85.2)	1.13 (0.59-2.17)	0.709	0.76 (0.41-1.40)	0.375	0.90 (0.58-1.40)	0.634	0.91 (0.60-1.36)	0.639	0.83 (0.49-1.19)	0.801
rs2221903	TT	231 (79.7)	90 (77.6)	83 (78.3)	271 (74.0)	-		-		-		-		-	
	CT	52 (17.9)	24 (20.7)	21 (19.8)	80 (21.9)	1.19 (0.69-2.04)	0.539	1.12 (0.64-1.98)	0.685	1.31 (0.89-1.94)	0.173	1.25 (0.87-1.79)	0.223	1.08 (0.53-1.55)	0.459
	CC	7 (2.4)	2 (1.7)	2 (1.9)	15 (4.1)	0.73 (0.15-3.60)	0.701	0.80 (0.16-3.91)	0.777	1.83 (0.73-4.56)	0.190	1.41 (0.59-3.41)	0.441	1.19 (0.41-2.87)	0.503
	C	59 (20.3)	26 (22.4)	23 (21.7)	95 (26.0)	1.13 (0.67-1.91)	0.643	1.09 (0.63-1.87)	0.769	1.37 (0.95-1.99)	0.092	1.27 (0.90-1.79)	0.171	1.08 (0.81-1.48)	0.311

OR<sub>1</sub>: NAG cases compared with controls; OR<sub>2</sub>: AG cases compared with controls; OR<sub>3</sub>: IM cases compared with controls; OR<sub>4</sub>: Total gastric precancerous lesions cases compared with controls; OR<sub>5</sub>: Adjusted by age, gender, BMI, drinking status, smoking status, daily salt intake and region. SNPs: Single nucleotide polymorphisms; NAG: Non-atrophic gastritis; AG: Atrophic gastritis; IM: Intestinal metaplasia.

**Table 5** Haplotype analysis of polymorphisms in patients and controls

SNPs	Haplo- type	Control (n = 290, %)	NAG (n = 116, %)	AG (n = 106, %)	IM (n = 366, %)	$\chi^2_{.1}$	$P_1$ value	OR <sub>1</sub>	$\chi^2_{.2}$	$P_2$ value	OR <sub>2</sub>	$\chi^2_{.3}$	$P_3$ value	OR <sub>3</sub>
rs90771 5'  rs12508 721	CC	0.496	0.543	0.575	0.571	0.713	0.397	1.20 (0.78- 1.86)	1.936	0.164	1.37 (0.88- 2.15)	3.612	0.057	1.35 (1.00- 1.84)
	CT	0.066	0.060	0.057	0.071	0.037	0.847	1.09 (0.45- 2.67)	0.104	0.747	1.17 (0.45- 3.01)	0.077	0.781	0.92 (0.50- 1.69)
	TC	0.163	0.138	0.047	0.087	0.368	0.544	1.21 (0.66- 2.23)	8.984	0.003	3.91 (1.51- 10.11)	8.509	0.004	2.02 (1.25- 3.26)
	TT	0.275	0.259	0.321	0.271	0.125	0.724	1.09 (0.67- 1.78)	0.763	0.382	0.81 (0.50- 1.31)	0.024	0.878	1.03 (0.73- 1.45)
rs22219 03'  rs90771 5	CC	0.128	0.129	0.123	0.158	0.002	0.963	0.99 (0.52- 1.87)	0.017	0.896	1.05 (0.53- 2.06)	1.264	0.264	0.78 (0.50- 1.21)
	CT	0.006	0.026	0.019	0.014	2.450	0.118	0.26 (0.04- 1.59)	1.113	0.292	0.36 (0.05- 2.60)	0.701	0.404	0.50 (0.10- 2.60)
	TC	0.434	0.474	0.509	0.484	0.527	0.468	0.85 (0.55- 1.31)	1.759	0.185	0.74 (0.47- 1.16)	1.571	0.210	0.82 (0.60- 1.12)
	TT	0.432	0.371	0.349	0.344	1.244	0.265	1.29 (0.83- 2.00)	2.158	0.142	1.41 (0.89- 2.24)	5.157	0.023	1.44 (1.05- 1.98)

Haplotype of rs907715(C/T), rs2221903 (T/C) and rs12508721(C/T). OR<sub>1</sub>: NAG cases compared with controls; OR<sub>2</sub>: AG cases compared with controls; OR<sub>3</sub>: IM cases compared with controls. SNPs: Single nucleotide polymorphisms; NAG: Non-atrophic gastritis; AG: Atrophic gastritis; IM: Intestinal metaplasia.

**Figure 2** Interleukin-21 mRNA expression level in six intestinal epithelium tissues among three rs907715 genotypes.**Figure 3** Interleukin-21 mRNA expression level in six non-atrophic gastritis tissues among three rs907715 genotypes.



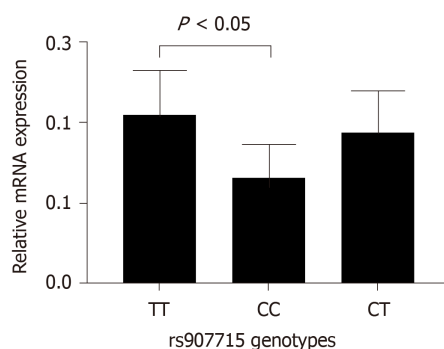


Figure 4 Interleukin-21 mRNA expression level in six atrophic gastritis tissues among three rs907715 genotypes.

## ARTICLE HIGHLIGHTS

### Research background

Previous studies have found that interleukin-21 (*IL-21*) may be associated with the risk of gastric precancerous lesions, and single nucleotide (SNPs) of the *IL-21* gene are associated with various diseases or cancer. Clarifying the possible role of *IL-21* SNPs (rs907715, rs2221903 and rs12508721) in gastric precancerous lesions is of great significance in preventing the development of gastric cancer.

### Research motivation

However, no studies have examined the possible role of *IL-21* SNPs (rs907715, rs2221903 and rs12508721) in gastric precancerous lesions.

### Research objectives

Therefore, the present study explored the associations between SNPs of *IL-21* (rs907715, rs2221903 and rs12508721) and risk of gastric precancerous lesions in a north western Chinese population, which may help clarify the etiology of gastric cancer and provide new targets for therapeutic interventions.

### Research methods

Gastric precancerous lesions were confirmed by endoscopic examination and categorized as non-atrophic gastritis, atrophic gastritis, and intestinal metaplasia. Three SNPs of *IL-21* (rs907715, rs2221903 and rs12508721) were genotyped using polymerase chain reaction–ligase detection reaction in 588 cases and 290 healthy controls. Descriptive statistic and logistic regression were used for data analyses.

### Research results

We found an association between *IL-21* rs907715 polymorphism and gastric precancerous lesions. *IL-21* rs907715 genotype CC and C frequencies in patients with gastric precancerous lesions were higher than in controls. SNP rs907715 increased in CC and C genotypes were associated with intestinal metaplasia patients when examined separately. However, the exact role of rs907715 in development of gastric precancerous lesions at a molecular level remains to be studied.

### Research conclusions

In conclusion, our findings indicate that SNP rs907715 of *IL-21* gene is associated with gastric precancerous lesions.

### Research perspectives

If confirmed by other studies, the results of our study suggest that *IL-21* rs907715 polymorphisms may shed light on the etiology of precancerous lesions.

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