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Association between interleukin gene polymorphisms and susceptibility to gastric cancer in the Qinghai population

Xiaoyan Song[1,*], Dongmei Wang[2,*], Baji Ben[1], Chenghua Xiao[1], Liyan Bai[1], Han Xiao[3], Wenyan Zhang[1], Wanchao Li[4], Jingying Jia[4] and Yujuan Qi[1]

Abstract

Objective: To investigate the associations between interleukin (IL) gene polymorphisms and susceptibility to gastric cancer in the Qinghai population, China.

Methods: Patients with gastric cancer and cancer-free controls were enrolled into the study from Qinghai Provincial People's Hospital between September 2016 and September 2018. Single nucleotide polymorphisms (SNPs) were genotyped with the Sequenom MassARRAY® SNP genotype system. The Hardy–Weinberg equilibrium in allele and genotype frequencies, and general characteristics between patients with gastric cancer and cancer-free controls, were evaluated using χ^2-test. Potential associations between interleukin gene variants and the risk of gastric cancer were analysed by logistic regression.

Results: Among eight candidate SNPs, the allele and genotype frequency distribution of IL-1B rs1143634 polymorphism was significantly different between patients with gastric cancer ($n = 190$) and cancer-free controls ($n = 186$). The IL-1B rs1143634 GA genotype and IL-1B rs1143634 GA + AA genotype were associated with a reduced risk of gastric cancer, however, the remaining SNPs were not statistically associated with gastric cancer risk in the Qinghai population.

[1]Department of Medical Oncology, Qinghai Provincial People's Hospital, Xining, China
[2]Department of Oncology, Affiliated Hospital of Heze Medical College, Heze, China
[3]Department of Medical Oncology, Qinghai University Affiliated Hospital, Xining, China
[4]Graduate School, Qinghai University, Xining, China

*These authors contributed equally to this work.

Corresponding author:
Yujuan Qi, Department of Medical Oncology, Qinghai Provincial People's Hospital, 2 Gonghe Road, Chengdong District, Xining, Qinghai, 810007, China.
Email: qiyujuanxn@outlook.com

Conclusion: The IL-1B rs1143634 polymorphism might be associated with a decreased risk of gastric cancer, and may be a protective factor against gastric cancer.

Keywords
Gastric cancer, susceptibility, interleukin (IL) genes, polymorphisms, IL-1B rs1143634, cancer risk

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Introduction

In 2018, approximately 18.1 million new cancer cases and 9.6 million cancer deaths were reported worldwide.[1] Gastric cancer is considered to be the fourth most common malignancy and the second highest cause of cancer death globally,[2] with varying incidence rates between different regions.[3] More than half of gastric cancer cases are reported in developing countries, and particularly in East Asia, including China.[2] The development of gastric cancer is a complex multistep and multifactorial process,[4] caused by a combination of environmental factors, such as *Helicobacter pylori*, Epstein-Barr Virus (EBV) infection, dietary habits, and genetic factors, including genetic alterations and epigenetic modifications.[2,5] Research is increasingly illustrating the importance of microorganisms in the development of gastric cancer.[6,7] Moreover, genetic factors, shown to be closely associated with gastric cancer, are also attracting growing attention.[8,9] Thus, exploring potential underlying genetic factors in gastric cancer may help in the development of effective treatments, and is of great clinical concern.

Chronic inflammation is a significant feature of gastric cancer.[10] As important mediators of the immune system, cytokines play a crucial role in cell proliferation, tissue development, gene expression, DNA repair and inflammation,[11] and they are considered to be the significant link between inflammation and cancer.[12] The chronic inflammation associated with gastric cancer development involves proinflammatory factors, such as interleukin (IL)-1B, IL-8, and tumour necrosis factor (TNF)-α, and also anti-inflammatory factors, such as IL-10. Several studies have reported that IL gene polymorphisms are associated with gastric carcinogenesis, and may influence the susceptibility to gastric cancer. For example, a significant positive association between IL-1B +3954 genotype distribution and gastric cancer was observed in the Iranian population, and the IL-1B gene polymorphism was found to be an important risk factor for gastric cancer.[13] Results of a case–control study suggested that the IL-10 C819T polymorphism was associated with an increased risk of gastric cancer in co-dominant, dominant, and recessive models.[14] Less direct associations have also been suggested. For example, Ying et al.[4] indicated that the effects of the IL-1B 31 polymorphism on gastric cancer susceptibility rely largely on the presence of *H. pylori*. Therefore, it is imperative to further investigate the relationship between IL polymorphisms and gastric cancer, to illustrate their specific role in gastric cancer.

Qinghai, China is located on the Qinghai-Tibet plateau, and is situated in a multi-ethnic region that mainly includes Han, Tibetan, Hui, and Mongolian ethnicities. The incidence of gastric cancer in the Qinghai area is relatively high, possibly due to factors such as race, geographical location, and the environment.[15] The aim of the present case–control study was to investigate a potential correlation between IL polymorphisms and susceptibility to gastric cancer in the Qinghai population, by analysing the

association between gastric cancer and IL-1B rs1143627, IL-1B rs1143634, IL-8 rs4073, IL-10 rs1800896, IL-16 rs4778889, IL-18 rs917997, IL-22 rs1179251, and IL-32 rs2015620 in a Qinghai study population of patients with gastric cancer and cancer-free controls.

Patients and methods

Study population

This observational, cross-sectional case–control study included patients with gastric cancer and cancer-free controls, aged between 18 and 70 years, recruited from Qinghai Provincial People's Hospital, Qinghai Province, China, between September 2016 and September 2018. All study participants were long-term residents of Qinghai Province, China. Inclusion criteria were: availability of tissue samples obtained from surgical or endoscopic examination, and new diagnosis of gastric cancer based on postoperative pathology data. Non-Qinghai residents or patients with benign gastric lesions and other malignant tumours were excluded. Sex- and age-matched (±3 years) cancer-free controls were selected from health screening program participants with complete clinical information and without personal or immediate family history of gastric cancer. Demographic and clinical data were collected, including age, sex, nationality, smoking status, drinking status, presence of *H. pylori* infection, and family history of cancer. The study was approved by the Ethics Committee of Qinghai Provincial People's Hospital, and written informed consent was obtained from all participants.

DNA extraction, PCR amplification and genotyping

Peripheral venous blood (5 ml) was collected from each participant into ethylenediamine tetra-acetic acid anticoagulant tubes and stored at –80 °C prior to use. Genomic DNA was extracted using TIANamp Blood DNA Kits (Tiangen, Beijing, China). The IL single nucleotide polymorphism (SNP) genotypes were then determined using a Sequenom MassARRAY® SNP genotype system (Sequenom, San Diego, CA, USA). The specific IL SNP primer sequences (Sangon, Shanghai, China), amplicon lengths and genotypes are described in Table 1. Genomic DNA samples were quantitatively diluted and placed into wells of a 384-well plate with the designed sequence shown in Table 1. Target sequences were then amplified by polymerase chain reaction (PCR) in a total reaction volume of 5 µl containing 20–50 ng DNA, 10 × PCR buffer (iPLEX GOLD Reagent Kit, Agena Bioscience, Beijing, China), 0.4 µl $MgCl_2$ (25 mM), 0.1 µl dNTPs (25 mM), 0.1 µl HotStar Taq DNA polymerase (5 U/µl; Agena Bioscience), 1.9 µl H_2O, and 1 µl PCR primer mix. The PCR conditions were as follows: an initial extension at 94 °C for 4 min, followed by 45 cycles of 94 °C for 20 s, 56 °C for 30 s, and 72 °C for 60 s, final extension at 72 °C for 3 min, then held at 4 °C. The PCR products were treated with alkaline phosphatase to remove any remaining dNTPs, after which, a single-base extension reaction was performed under the following conditions: 94 °C for 30 s, 94 °C for 5 s, 52 °C for 5 s, and 80 °C for 5 s. Following resin purification, the reaction products were moved into SpectroCHIP chips (Sequenom), and genotypes were detected using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Sequenom MassARRAY®).

Statistical analyses

Data are presented as *n* (%) prevalence or mean ± SD. Statistical analyses were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA). χ^2-test

Table 1. Primer sequences, amplicon lengths and genotypes of interleukin gene polymorphisms.

SNP	2nd-PCRP[a] 1st-PCRP[b]	AMP[c]	UEP_SEQ[d]	Genotype
rs1143627	ACGTTGGATGCCTCGAAGAGGTTTGGTATC ACGTTGGATGTCTCAGCCTCCTACTTCTGC	98	TTCTCCCTCGCTGTTTTTAT	AG, AA, GG
rs1143634	ACGTTGGATGGTGCTCCACATTTCAGAACC ACGTTGGATGAGTGATCGTACAGGTGCATC	100	ACATTTCAGAACCTATCTTCTT	GA, GG, AA
rs4073	ACGTTGGATGCTGAAGCTCCACAATTTGGT ACGTTGGATGGCCACTCTAGTACTATATCTG	118	CACAATTTGGTGAATTATCAA	TA, TT, AA
rs1800896	ACGTTGGATGATTCCATGGAGGCTGGATAG ACGTTGGATGGACAACACTACTAAGGCTTC	107	tCCTATCCCTACTTCCCC	CT, CC, TT
rs4778889	ACGTTGGATGAGTCCCTCCACACTCAAAGC ACGTTGGATGCATGGGCTCATACTGTTGAC	99	gCAAAGCCTTTTGTTCCTATCA	CT, CC, TT
rs917997	ACGTTGGATGCTCAGACTTCTTTTGGCCAC ACGTTGGATGAGCTAAGGTCAAAACGCTGG	113	ATGCTAGAACCAAGCTAT	CT, CC, TT
rs1179251	ACGTTGGATGACCTGCATTCTAGCCCTATC ACGTTGGATGGGTTGGGATCTTAGCTTGTC	101	ACTGACCATCCCCAGAAT	CG, CC, GG
rs2015620	ACGTTGGATGAAGTTCTCCAGCCAGTGGTC ACGTTGGATGAAGAATTTAGGCGGCAGTGG	102	GTGGTCTCAACTCAATCTTC	TA, TT, AA

SNP, single nucleotide polymorphism.

[a]2nd-PCRP, secondary (reverse) amplification primer (including secondary tag);

[b]1st-PCRP, primary (forward) amplification primer (including primer tag);

[c]AMP, amplicon length (in bases; including primer tags and maximum SNP sequence length);

[d]UEP_SEQ, extend primer sequence (used in the single-base extension reaction for genotype identification).

was used to evaluate the Hardy–Weinberg equilibrium (HWE) in allele and genotype frequencies, and categorical data regarding general characteristics between patients with gastric cancer and cancer-free controls. The odds ratios (ORs) and 95% confidence intervals (CIs) from unconditional logistic regression were used to assess the potential associations between genetic variants of interleukin genes and gastric cancer risk. ORs were adjusted according to age, sex, nationality, *H. pylori* infection, tobacco smoking, alcohol drinking and family history of cancer. A P-value < 0.05 was defined as statistically significant.

Results

Demographic and clinical characteristics in patients with gastric cancer versus healthy controls

A total of 190 patients with gastric cancer and 186 cancer-free controls from the Qinghai population were included. Statistically significant differences were found in age, sex, *H. pylori* infection status and nationality between patients with gastric cancer and cancer-free controls ($P < 0.05$; Table 2), while no significant between-group differences were found in

Table 2. Demographic and clinical characteristics of patients with gastric cancer and cancer-free controls from the Qinghai region.

Characteristic	Study group		χ^2-value	Statistical significance
	Cases *n* (%)	Controls *n* (%)		
Number	190 (50.53)	186 (49.47)		
Age			8.987	$P < 0.001$
Years	56.76 ± 11.584	48.26 ± 5.917		
<60 years	108 (56.84)	179 (96.24)		
≥60 years	82 (43.16)	7 (3.76)		
Sex			21.476	$P < 0.001$
Male	148 (77.89)	103 (55.38)		
Female	42 (22.11)	83 (44.62)		
Nationality			10.413	$P = 0.001$
Han population	124 (65.26)	149 (80.11)		
Minority nationalities	66 (34.74)	37 (19.89)		
Tobacco smoking			0.251	NS
Yes	68 (35.79)	62 (33.33)		
No	122 (64.21)	124 (66.67)		
Alcohol drinking			0.638	NS
Yes	68 (35.79)	74 (39.78)		
No	122 (64.21)	112 (60.22)		
Helicobacter pylori infection			25.094	$P < 0.001$
Positive	152 (80.00)	104 (55.91)		
Negative	38 (20.00)	82 (44.09)		
Family history of cancer			2.465	NS
Yes	17 (8.95)	9 (4.84)		
No	173 (91.05)	177 (95.16)		

Data presented as *n* (%) prevalence or mean ± SD.
NS, no statistically significant between-group difference ($P > 0.05$; χ^2-test).

tobacco smoking, alcohol drinking, and family history of cancer ($P > 0.05$; Table 2).

Allele and genotype frequency distribution

The genotype and allele frequencies of eight SNPs (IL-1B rs1143627, IL-1B rs1143634, IL-8 rs4073, IL-10 rs1800896, IL-16 rs4778889, IL-18 rs917997, IL-22 rs1179251 and IL-32 rs2015620) in patients with gastric cancer and cancer-free controls are summarized in Table 3. The genotype frequencies fitted the HWE in gastric cancer cases and cancer-free controls except for IL-1B rs1143634. The IL-1B rs1143634 SNP showed statistically significant differences in allele frequency distributions between gastric cancer cases (G, 93.42%; A, 6.58%) and cancer-free controls (G, 97.85%; A, 2.15%; $\chi^2 = 8.786$, $P = 0.003$), and differences in genotype frequency distributions between gastric cancer cases (GA, 10.00%; GG, 88.42%; AA, 1.58%) and cancer-free controls (GA, 4.30%; GG, 95.70%; AA, 0.00%; $\chi^2 = 7.311$, $P = 0.016$). No statistically significant between-group differences in genotype or allele frequencies were observed for the other SNPs (all $P > 0.05$; Table 3).

Association between interleukin gene polymorphisms and gastric cancer risk

Logistic regression analyses of the potential associations between IL gene polymorphisms and risk of gastric cancer are shown in Table 4. The IL-1B rs1143634 GA genotype (OR 0.242, 95% CI 0.088, 0.670; $P = 0.006$) and IL-1B rs1143634 GA + AA genotype (OR 0.227, 95% CI 0.084, 0.618; $P = 0.004$) were found to be associated with a reduced risk of gastric cancer. The other investigated SNPs were not found to be statistically associated with gastric cancer risk in the Qinghai population ($P > 0.05$).

Discussion

Gastric cancer remains one of the most common cancers, accounting for approximately 424 000 new cases annually in China, and its incidences in men and women are the fifth and third highest, respectively, among all malignant tumours in China.[16] Inflammatory factors are increasingly recognized as being associated with the pathogenesis of gastric cancer, with numerous studies reporting a relationship between chronic inflammation and gastric cancer occurrence and development.[17–19] Environmental and genetic factors are also involved in gastric cancer development. In the present study, the association between eight IL SNPs and the risk of gastric cancer was investigated, and a significant difference was observed in the allele and genotype frequency distribution of the IL-1B rs1143634 gene polymorphism between patients with gastric cancer and cancer-free controls. In addition, the IL-1B rs1143634 GA and AA + GA genotypes were found to be statistically associated with a reduced susceptibility to gastric cancer compared with GG genotype carriers. To the best of our knowledge, this is the first report on the vital roles of IL gene polymorphisms in gastric cancer among the Qinghai population, China.

Interleukin-1β, encoded by *IL-1B*, is a member of the interleukin 1 family of cytokines, and is both a pro-inflammatory factor produced by activated macrophages and other cell types, and an effective inhibitor of gastric acid secretion.[20,21] The *IL-1B* gene is located on chromosome 2q13 in humans.[22] IL-1B-31 (rs1143627) polymorphisms in the promoter region and +3954 (rs1143634) polymorphisms in exon 5 are two functional SNPs of the *IL-B* gene.[22,23] Two previous studies reported an association between the IL-1B +3954 C/T polymorphism and risk of gastric cancer.[13,24] However, another study showed no significant

Table 3. Genotype and allele frequencies of interleukin gene polymorphisms in patients with gastric cancer and healthy controls from the Qinghai region.

SNP genotype	Study group		χ^2-value	Statistical significance
	Cases $n = 190$	Controls $n = 186$		
IL-1B rs1143627				
AG	95 (50.00)	99 (53.22)	0.627	NS
AA	46 (24.21)	39 (20.97)		
GG	49 (25.79)	48 (25.81)		
A allele	187 (49.21)	177 (47.58)	0.2	NS
G allele	193 (50.79)	195 (52.42)		
IL-1B rs1143634				
GA	19 (10.00)	8 (4.30)	7.311	$P = 0.016$[a]
GG	168 (88.42)	178 (95.70)		
AA	3 (1.58)	0 (0.00)		
G allele	355 (93.42)	364 (97.85)	8.786	$P = 0.003$
A allele	25 (6.58)	8 (2.15)		
IL-8 rs4073				
TA	88 (46.32)	89 (47.85)	0.143	NS
TT	72 (37.89)	67 (36.02)		
AA	30 (15.79)	30 (16.13)		
T allele	232 (61.05)	223 (59.95)	0.096	NS
A allele	148 (38.95)	149 (40.05)		
IL-10 rs1800896				
CT	30 (15.79)	31 (16.67)	0.445	NS[a]
CC	2 (1.05)	1 (0.54)		
TT	158 (83.16)	154 (82.80)		
C allele	34 (8.95)	33 (8.87)	0.001	NS
T allele	346 (91.05)	339 (91.13)		
IL-16 rs4778889				
CT	75 (39.47)	83 (44.62)	1.055	NS
CC	12 (6.32)	10 (5.38)		
TT	103 (54.21)	93 (50.00)		
C allele	99 (26.05)	103 (27.69)	0.256	NS
T allele	281 (73.95)	269 (72.31)		
IL-18 rs917997				
CT	83 (43.68)	92 (49.46)	1.294	NS
CC	56 (29.47)	48 (25.81)		
TT	51 (26.84)	46 (24.73)		
C allele	195 (51.32)	188 (50.54)	0.046	NS
T allele	185 (48.68)	184 (49.46)		
IL-22 rs1179251				
CG	73 (38.42)	89 (47.85)	4.878	NS
CC	94 (49.47)	84 (45.16)		
GG	23 (12.11)	13 (6.99)		
C allele	261 (68.68)	257 (69.09)	0.014	NS
G allele	119 (31.32)	115 (30.91)		

(continued)

Table 3. Continued.

SNP genotype	Study group		χ^2-value	Statistical significance
	Cases $n = 190$	Controls $n = 186$		
IL-32 rs2015620				
TA	84 (44.21)	94 (50.54)	1.579	NS
TT	55 (28.95)	46 (24.73)		
AA	51 (26.84)	46 (24.73)		
T allele	194 (51.05)	186 (50.00)	0.083	NS
A allele	186 (48.95)	186 (50.00)		

Data presented as *n* (%) prevalence.
SNP, single nucleotide polymorphism.
[a]Analysed using Fisher's exact test.
NS, no statistically significant between-group difference ($P > 0.05$; χ^2-test).

association between IL-1B rs1143627 and rs1143634 polymorphisms and gastric cancer,[25] and a meta-analysis revealed that IL-1B 31 C > T polymorphism was not significantly associated with gastric cancer risk.[4] In the present case–controlled study, subjects carrying the IL-1B rs1143634 GA or AA + GA genotype had a reduced risk of gastric cancer, suggesting that these genotypes may be protective against gastric cancer. However, the genotype frequencies of IL-1B rs1143634 did not conform to the HWE law, probably due to the small sample size. Therefore, the sample size should be expanded in a subsequent study to further confirm these results. No statistically significant difference was found between patients with gastric cancer and cancer-free controls in terms of the IL-1B rs1143627 polymorphisms.

Interleukin-8 is a chemokine secreted by a variety of cells, such as neutrophils, monocytes, endothelial cells and epithelial cells. As a neutrophil activator, IL-8 can promote the angiogenic response of endothelial cells, recruitment of neutrophils to a tumour site, and the proliferation, survival, and migration of tumour cells in tumour progression.[26] The *IL-8* gene is located on chromosome 4q12-q13, comprising four exons and three introns, and the common polymorphism is IL8-251T/A (rs4073) at the promoter region.[27–29] Chang et al.[30] found that a combination of *H. pylori* infection and the IL-8 -251 T > A polymorphism might increase the risk of severe atrophic gastritis and gastric cancer in a Korean population, and results of a meta-analysis indicated that the IL-8 -251 AA genotype was associated with the overall risk of developing gastric cancer and may increase the overall gastric cancer susceptibility in Asian populations.[31] No significant relationship was revealed between IL8 rs4073 and gastric cancer in the present Qinghai population, which concurred with a previous report that the IL-8 rs4073 polymorphism was not significantly related to risk of gastric cancer in a high-risk Chinese population.[25]

Interleukin-10, a multifunctional cytokine produced by immune cells in viral infections, can modulate the function of immune cells and protect the host from tissue damage during the acute phase of the immune response.[32] Furthermore, it is vital for the maintenance of normal physiology and suppression of cancer development, and keeps a balance between proinflammatory and anti-inflammatory

Table 4. Association between gastric cancer risk and interleukin gene polymorphisms in the Qinghai population.

SNP genotype	Study group		OR (95% CIs)	Statistical significance
	Cases $n = 190$	Controls $n = 186$		
IL-1B rs1143627				
AA	46 (24.21)	39 (20.97)	1.00	
AG	95 (50.00)	99 (53.22)	1.700 (0.912, 3.168)	NS
GG	49 (25.79)	48 (25.81)	1.746 (0.861, 3.544)	NS
AG+GG	144 (75.79)	147 (79.03)	1.715 (0.949, 3.099)	NS
IL-1B rs1143634				
GG	168 (88.42)	178 (95.70)	1.00	
GA	19 (10.00)	8 (4.30)	0.242 (0.088, 0.670)	$P = 0.006$
AA	3 (1.58)	0 (0.00)	0.000 (0.000)	NS
GA+AA	22 (11.58)	8 (4.30)	0.227 (0.084, 0.618)	$P = 0.004$
IL-8 rs4073				
TT	72 (37.89)	67 (36.02)	1.00	
TA	88 (46.32)	89 (47.85)	0.684 (0.327, 1.433)	NS
AA	30 (15.79)	30 (16.13)	0.968 (0.475, 1.974)	NS
TA+AA	118 (62.11)	119 (63.98)	1.427 (0.860, 2.368)	NS
IL-10 rs1800896				
CC	2 (1.05)	1 (0.54)	1.00	
CT	30 (15.79)	31 (16.67)	4.238 (0.243, 73.902)	NS
TT	158 (83.16)	154 (82.80)	3.17 (0.192, 52.317)	NS
CT+TT	188 (98.95)	185 (99.46)	3.309 (0.200, 54.640)	NS
IL-16 rs4778889				
CC	12 (6.32)	10 (5.38)	1.00	
CT	75 (39.47)	83 (44.62)	1.088 (0.388, 3.048)	NS
TT	103 (54.21)	93 (50.00)	0.941 (0.340, 2.603)	NS
CT+TT	178 (93.68)	176 (94.62)	1.004 (0.372, 2.708)	NS
IL-18 rs917997				
CC	56 (29.47)	48 (25.81)	1.00	
CT	83 (43.68)	92 (49.46)	1.343 (0.739, 2.440)	NS
TT	51 (26.84)	46 (24.73)	0.744 (0.381, 1.454)	NS
CT+TT	134 (70.53)	138 (74.19)	1.080 (0.622, 1.873)	NS
IL-22 rs1179251				
CC	94 (49.47)	84 (45.16)	1.00	
CG	73 (38.42)	89 (47.85)	1.687 (0.997, 2.853)	NS
GG	23 (12.11)	13 (6.99)	0.565 (0.234, 1.366)	NS
CG+GG	96 (50.53)	102 (54.84)	1.378 (0.841, 2.257)	NS
IL-32 rs2015620				
TT	55 (28.95)	46 (24.73)	1.00	
TA	84 (44.21)	94 (50.54)	1.363 (0.754, 2.464)	NS
AA	51 (26.84)	46 (24.73)	1.409 (0.723, 2.748)	NS
TA+AA	135 (71.05)	140 (75.27)	1.379 (0.793, 2.397)	NS

Data presented as *n* (%) prevalence.

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

NS, no statistically significant correlation ($P > 0.05$).

signals provided by different T-cell populations.[33] The *IL-10* gene is located on chromosome 1 at 1q31-32, and IL-10-1082 (G/A), -819 (C/T), -592 (C/A) are three of the most studied SNPs.[34,35] In a meta-analysis, IL-10 gene polymorphisms were suggested to be associated with cancer risk in the Chinese population.[36] Results from a clinical study revealed that the IL-10-1082 gene was a susceptibility gene for gastric cancer,[37] and the IL-10-1082 A/G (rs1800896) polymorphism has been suggested to contribute to gastric cancer susceptibility, particularly among Asians.[38] In the present study population, no significant association was found between the IL-10 rs1800896 polymorphism and gastric cancer risk, which concurs with previous research.[25]

Interleukin-16 is a multifunctional proinflammatory cytokine and lymphocyte chemoattractant that not only regulates the inflammatory process, but also regulates tumorigenesis.[39,40] The *IL-16* gene is located on chromosome 15q26.3 of the human genome,[41] and the rs4778889 polymorphism is located at position -295 in the promoter region of this gene, which is related to gene expression.[42] One study reported that the IL-16 rs4778889 CC genotype was related with elevated risk of non-cardia gastric cancer in the Chinese population.[43] However, the results of a meta-analysis suggested there was no statistically significant association between the IL-16 rs4778889 T/C polymorphism and risk of cancer in the Asian population.[44] The present study also failed to reveal any significant association between IL-16 rs4778889 and risk of gastric cancer, suggesting that the IL-16 rs4778889 polymorphism may not affect gastric cancer susceptibility.

Interleukin-18, as a member of the IL-1 family of cytokines, is a pleiotropic immune regulator that plays a powerful pro-inflammatory role by inducing interferon-γ.[45] As the immune-stimulating effect of IL-18 has antitumour properties, IL-18 has been recommended as a new adjuvant therapy for cancer.[46] The IL-18 receptor (IL-18R) is composed of an IL-18R accessory protein (IL-18RAP) and IL-18R1 protein, and the IL-18RAP rs917997 is located at 1.5 kb downstream of IL-18RAP.[46–48] The IL-18RAP rs917997 C allele may be a protective factor against Barrett's oesophagus and oesophageal adenocarcinoma,[49] however, the result of another study showed no association between the IL-18RAP rs917997 C > T polymorphisms and the risk of oesophageal squamous cell carcinoma.[50] Wang et al.[25] found that the IL-18RAP rs917997 G allele might be protective against gastric cancer in a high-risk Chinese population. In the present study, the allele and genotype frequency distributions of the IL-18RAP rs917997 polymorphism were not significantly different between patients with gastric cancer and cancer-free controls, and there was no relationship between the IL-18RAP rs917997 polymorphism and gastric cancer risk. This may have been due to differences in race, region, and genotype in the study population, and also the relatively small size of the sample.

Interleukin-22 is a member of the IL-10 family of cytokines that includes IL-10, IL-19, IL-20, IL-24, IL-26, IL-28 and IL-29.[51] IL-22 plays a crucial role in inflammation and tumorigenesis, and the IL-22 rs1179251 polymorphism is associated with increased risk of cancer.[52–54] The IL-22 rs1179251 polymorphism has been significantly associated with an increased risk of gastric cancer.[55] In addition, IL-22 rs1179251 was shown to be related to advanced stages, lymph node metastases, and distant metastases of gastric cancer, suggesting it may influence gastric cancer progression.[55]

The human *IL-32* gene resides on chromosome 16 p13.3 and comprises eight small exons.[56] Although IL-32 was originally reported to be a pro-inflammatory cytokine in 2005,[57] some studies revealed IL-32 to be involved in cancer cell growth and

metastasis, by regulating nuclear factor (NF)-κB,[58–61] which is a transcription factor and modulates growth factors and apoptosis inhibitors. IL-32 has also been implicated in cancer cell growth through its interaction with signal transducer and activator of transcription 3 (STAT3) signalling,[58] which has been shown to promote cancer development.[62] Furthermore, IL-32 was reported to promote colon cancer cell death via regulation of the p38/mitogen-activated protein kinase (MAPK) signalling pathway.[63] The above research indicates that IL-32 is involved in multiple cancers by regulating NF-κB, STAT3 and MAPK signalling pathways.[64] IL-32 is also reported to be involved in the occurrence and progression of gastric cancer. For example, Tsai et al.[59] suggested that IL-32 was associated with increasing human gastric cancer cell invasion, contributing to gastric cancer progression and metastasis. Wang et al.[25] observed that the IL-32 rs2015620 A allele was associated with increasing risk of gastric cancer, suggesting that the IL-32 rs2015620 polymorphism may be involved in gastric cancer development, and in particular, advanced gastric lesions. These studies reported the possible associations of IL-22 rs1179251 and IL-32 rs2015620 with the susceptibility to gastric cancer, and their possible participation in gastric cancer progression. However, the present study found no statistically significant associations between the IL-22 or IL-32 polymorphisms and susceptibility to gastric cancer.

The above research results indicate the importance of IL in the occurrence and development of gastric cancer. In addition to these critical ILs, others, including IL-6, IL-17, IL-23, have also been shown to play an important role in gastric cancer. For example, translational levels of IL-17 and IL-23 have been shown to differ in the pathogenesis of different types of gastric neoplasms,[65] and IL ratios may be promising in the diagnosis of gastric cancer in humans.[66] Although the results of the present study may be limited by the single-centre setting and the relatively small Qinghai study population, many previously published reports have shown that abnormal IL expression in humans is related to gastric cancer. The results of the present study should be verified by future research involving larger sample sizes and different populations.

Conclusions

In conclusion, the present study results suggest that the IL-1B rs1143634 polymorphism may be an important factor in reducing the risk of gastric cancer in the Qinghai population, China. IL-8, IL-10, IL-16, IL-18RAP, IL-22 and IL-32 genetic polymorphisms may influence the susceptibility to gastric cancer, but no statistically significant association with gastric cancer was observed, possibly due to differences in race, geographical region, sample size and genotype methods between the present study and previous research.

Author contributions

Xiaoyan Song made substantial contributions to the study conception and design, and to data acquisition, analysis and interpretation; Dongmei Wang performed the experiments; Baji Ben, Chenghua Xiao and Liyan Bai were involved in drafting the manuscript or revising it critically for important intellectual content; Han Xiao, Wenyan Zhang, Wanchao Li and Jingying Jia gave final approval of the version to be published. Yujuan Qi agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Yujuan Qi https://orcid.org/0000-0002-0098-6813

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