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BRIEF ARTICLE

Associations between interleukin-1 polymorphisms and gastric cancers among three ethnicities

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Abstract

AIM: To investigate the associations between interleukin (IL)-1B and IL-1RN polymorphisms and gastric cancers among the Tibet, Hui and Han ethnicities.

METHODS: Genomic DNA was extracted from peripheral blood of 210, 205, and 202 healthy volunteers and from 155, 158, and 197 gastric cancer patients from the Tibet, Hui, and Han populations, respectively. Polymorphisms in *IL-1B* and *IL-1RN* were analyzed by denaturing high-performance liquid chromatography.

RESULTS: Carriers of the *IL-1B*-31 CC genotype had an increased risk of intestinal type gastric cancer [odds ratio (OR) = 2.17, P = 0.037] in the Tibet ethnicity. Carriers of the *IL-1B* 2/L genotype had an increased risk of both intestinal and diffuse types of gastric cancer (OR = 2.08, 2.31, P = 0.007, 0.016, respectively) in the Hui ethnicity. In the Han population, carriers of the *IL-1B*-31 CC, *IL-1B*-511CT, TT genotypes had increased risk of intestinal type gastric cancer (OR = 2.51, 2.74, 5.66, P = 0.005, 0.002, 0.000, respectively).

CONCLUSION: *IL-1B* and *IL-RN* genotypes may differentially contribute to gastric cancer among the Tibet, Hui, and Han ethnicities in the Qinghai area of China.

Key words: Gastric cancer; Interleukin-1B; Interleukin-1RN; Polymorphism; Risk of gastric cancer

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INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer-related death worldwide, and approximately 42% of these deaths occur in China[1,2]. Mortality of GC patients in China is the highest in the world, especially in the northwestern part of the country, which includes Qing-

hai province[3]. There are 56 different ethnicities living in China. The Han ethnicity represents the major ethnicity within Qinghai province, while the Tibet and Hui are minority nationalities. The incidence of GC in the Tibet and Hui populations is higher than that in the Han ethnicity. However, the study of minority ethnicities is not advanced due to fewer individuals and poorer economic conditions[4].

Interleukin (IL)-1B and IL-1RN belong to the *IL-1* gene cluster. The *IL-1* gene encodes both the glycoprotein IL-1β, which is a pro-inflammatory cytokine, and the *IL-1* receptor antagonist (IL-1Ra), which is an anti-inflammatory cytokine. *IL-1B* is a potent inhibitor of gastric acid secretion and plays a major role in both initiating and amplifying the inflammatory response to *Helicobacter pylori* (*H. pylori*) infection[5-7]. *IL-1RN* encodes the *IL-1Ra*, an anti-inflammatory cytokine that competitively binds to IL-1 receptors and modulates the potentially damaging effects of IL-1[7,8]. Two biallelic polymorphisms in the *IL-1B* gene have been described, both C-T base transitions found at positions-511 (C>T) and -31 (T>C) bp from the translation initiation codon. IL-1RN has a variable number of identical tandem repeats polymorphism of 86 bp in intron 2. To date, over 50 studies have reported on the association between *IL-1B* and *IL-1RN* polymorphisms and GC risk[5]. While some studies have reported that *IL-1B* and *IL-1RN* polymorphisms are associated with increased GC risk in both Caucasians and Asians[5,6,9,10], other studies have shown inverse associations, especially in Asians[11,12]. Two studies chose a single ethnicity population in two different regions with different prevalence rates of GC as their subjects[10,13]. However, no study has examined several different ethnicities in a single geographical area at the same time. Thus, our study is the first to report such an examination.

Here, we investigated the associations between *IL-1B*-31, *IL-1B*-511 and *IL-1RN* polymorphisms and GC risk among the Tibet, Hui and Han ethnicities in the Qinghai area of China.

MATERIALS AND METHODS

Study subjects

Three ethnicities (Tibet, Hui and Han) from the Qinghai province of China were included in this study. Healthy controls included 210 Tibet, 205 Hui and 202 Han individuals who were enrolled from the Hainan Tibet Ethnicity Autonomous Prefecture, Minhe Hui Ethnicity Autonomous County, and Xining city in Qinghai province, respectively. Between December 2008 and October 2011, 155, 158 and 197 Tibet, Hui and Han individuals, respectively, with GC were enrolled from the Affiliated Hospital of Qinghai University. All recruited healthy controls were from families that had lived for a long time in that locality, did not marry other ethnicities for at least three generations, and were not related to each other. Both the age and sex of the healthy controls were matched to the patients and are shown in Table 1. None of these subjects had a history of systemic lupus erythematosus, diabetes mellitus, rheumatoid arthritis, or inflammatory bowel disease. Subjects with a family history of any cancer were excluded. All patients were histologically confirmed as having noncardiac GC. Patients and controls were interviewed with regard to smoking status. Individuals who smoked once a day for over 1 year were defined as smokers. The presence of *H. pylori* infection in the sera of patients and controls was measured using an enzyme-linked immunosorbent assay (Anti-*H. pylori* enzyme immunoassay, Huamei Biotech Inc., China). This study was approved by the Clinical Research Ethics Committee of the Qinghai University of Medical Sciences, and all patients provided signed informed consent.

Analysis of the IL-1B-31, IL-1B-511 and IL1-RN polymorphisms

Genomic DNA was isolated from 5 mL of venous blood by the conventional proteinase K digestion and phenol/chloroform extraction method. Polymorphisms were analyzed by polymerase chain reaction (PCR)-based denaturing high-performance liquid chromatography (DHPLC). The corresponding primers have been by described by Lu *et al*[14] and are shown together with the PCR conditions, PCR annealing temperatures and DHPLC detection methods in Table 2. PCR was performed with a 25 mL reaction mixture containing 100 ng of genomic DNA, 1.0 mmol/L of primer, 0.2 mmol/L of dNTP, 2.0 mmol/L of $MgCl_2$, and 1.0 U Taq DNA polymerase in 1× reaction buffer (Promega, Madison, WI, United States). DHPLC analysis was performed on a Transgenomic WAVE System. The detailed genotyping process has been previously described[14]. The PCR products were applied to the DHPLC column at an optimal oven temperature and eluted with a linear acetonitrile gradient at a flow rate of 0.9 mL/min (Figure 1A). The genotypes identified by DHPLC analysis were further confirmed by DNA sequencing using the ABI Prism 377 DNA Sequencer. The sizes of *IL-1RN* PCR products were analyzed by DHPLC based on the relationship between elution time and base pair number of the fragment (Figure 1B).

H. pylori antibody assays

Enzyme-linked immunosorbent assay for detection of *H. pylori* was performed according to the manufacturer's instructions. After termination of the enzyme reaction, the absorbance at 630 nm was measured. Absorbance ratios (sample/negative control) equal to or greater than 2.1 were considered positive, and those below 2.1 were considered negative.

Statistical analysis

The data were analyzed using SPSS software (Version 13.0, SPSS, Chicago, IL, United States). The significance of the difference in the distribution of the polymorphisms among the different groups was calculated using the χ^2 test. All allelic distributions were examined for deviations from their corresponding Hardy-Weinberg

Table 1 Primer sequences, polymerase chain reaction and denaturing high-performance liquid chromatography conditions for detection of gene polymorphisms

Gene	Primer sequence	PCR annealing temperature (℃)	PCR product size (bp)	DHPLC application type	Oven temperature (℃)
IL-1B-31	F: AGAAGCTTCCACCAATACTC R: AGCACCTAGTTGTAAGGAAG	60	240	Mutation	59
IL-1B-511	F: TGGCATTGATCTGGTTCATC R: GTTTAGGAATCTTCCCACTT	58.5	306	Mutation	60.5
IL-1 RN	F: CCCCTCGAGCAACATCC R: GGTCAGAAGGGCAGAGA	59	270-442	VNTR	50.0

DHPLC: Denaturing high-performance liquid chromatography; VNTR: Variable number of identical tandem repeats; PCR: Polymerase chain reaction; IL: Interleukin.

Table 2 Selective characteristics and risk factors in patients with gastric cancer and controls from the Tibet, Hui and Han ethnicities *n* (%)

Variable		Tibet				Hui				Han			
		Cases (*n* = 155)	Controls (*n* = 210)	χ^2	*P* value	Cases (*n* = 158)	Controls (*n* = 205)	χ^2	*P* value	Cases (*n* = 197)	Controls (*n* = 202)	χ^2	*P* value
Age, yr	< 35	3 (1.94)	5 (2.38)	0.006	0.940	2 (1.27)	2 (0.980)	0.069	0.793	5 (2.54)	5 (2.48)	0.602	0.437
	35-60	82 (52.90)	110 (52.38)	0.010	0.921	75 (47.46)	102 (49.76)	0.187	0.665	98 (49.75)	106 (52.48)	0.297	0.586
	⩾ 60	70 (45.16)	95 (45.24)	0.000	0.988	81 (51.27)	101 (49.24)	0.142	0.706	94 (47.71)	91 (45.04)	0.285	0.593
Gender	Male	116 (74.84)	154 (73.33)	0.105	0.746	116 (73.42)	148 (71.20)	0.067	0.795	146 (74.62)	151 (74.75)	0.003	0.952
	Female	39 (25.16)	56 (26.67)			42 (26.58)	57 (28.80)			50 (25.38)	51 (25.25)		
Smoking	Yes	99 (63.87)	135 (64.29)	0.007	0.935	28 (17.71)	40 (19.51)	0.188	0.665	131 (66.50)	129 (63.86)	0.200	0.655
	No	56 (36.13)	75 (35.71)			130 (82.29)	165 (80.49)			66 (33.50)	73 (36.14)		
Hp	Positive	101 (65.16)	112 (53.33)	5.134	0.023	100 (63.29)	95 (46.34)	10.311	0.001	124 (62.94)	105 (51.98)	4.903	0.027
	Negative	54 (34.84)	98 (46.67)			58 (36.71)	110 (53.66)			73 (37.06)	97 (48.02)		

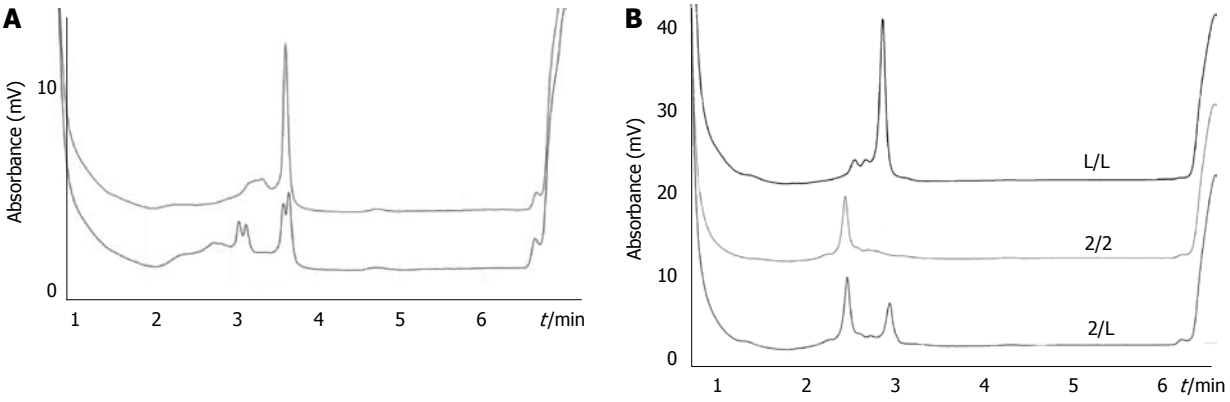

Figure 1 Typical denaturing high-performance liquid chromatography elution profiles for different genotypes. A: Representative denaturing high-performance liquid chromatography (DHPLC) profiles for different allelic polymerase chain reaction products containing the *interleukin-1B* (*IL-1B*)-311 C/T polymorphism site. In the first DHPLC, the CT genotype (lower panel) was discriminated from homozygous (upper panel). To determine the CC or TT genotype, the second DHPLC was run for the homozygous DNA mixed with a DNA sample known as the CC genotype. The profile of the CC genotype was unaltered, while that of the TT genotype changed into the same as the lower panel; B: DHPLC elution profiles of *IL-1RN* and *IL-1RN* variable number of identical tandem repeats were determined by elution time and base pair number of the fragment.

equilibrium. Multivariate logistic regression was used to obtain odds ratios (ORs) and 95%CI, adjusting for age, sex, smoking status and *H. pylori* infection. $P < 0.05$ (two-tailed) was considered statistically significant.

RESULTS

Clinical characteristics

The study population consisted of 210, 205 and 202 healthy controls and 155, 158 and 197 GC patients from the Tibet, Hui and Han ethnicities, respectively. Age, sex, smoking status, and *H. pylori* infection in the GC patients and control subjects are shown in Table 1. There were no statistically significant differences between the cases and controls with regard to age, sex, and smoking status in each ethnicity group. However, *H. pylori* infection was significantly higher in the cases compared to the controls ($P = 0.023$, 0.001 and 0.027, respectively) in each ethnicity group. The genotype frequencies of *IL-1B*-31, *IL-1B*-511 and *IL-1RN* in the controls in each ethnicity group were in agreement with the Hardy-Weinberg equilibrium ($P > 0.05$ for all).

Table 3 Genotype distributions of *interleukin-1B*-31, *interleukin-1B*-511 and *interleukin-1RN* gene polymorphisms among gastric cancer cases and controls from the Tibet, Hui and Han ethnicities *n* (%)

Genotype	Tibet				Hui				Han			
	Cases	Controls	OR (95%CI)[1]	*P* value	Cases	Controls	OR (95%CI)[1]	*P* value	Cases	Controls	OR (95%CI)[1]	*P* value
IL-1B-31												
TT	23 (14.84)	47 (22.38)	1		46 (29.11)	59 (28.78)	1		40 (20.30)	65 (32.18)	1	
CT	81 (52.26)	112 (53.33)	1.47 (0.81-2.66)	0.208	79 (50.00)	105 (51.22)	0.97 (0.58-1.62)	0.896	102 (51.77)	98 (48.52)	1.69 (1.03-2.76)	0.036
CC	51 (32.90)	51 (24.29)	2.10 (1.09-4.04)	0.027	33 (20.89)	41 (20.00)	1.03 (0.55-1.95)	0.919	55 (27.92)	39 (19.31)	2.29 (1.28-4.10)	0.005
IL-1B-511												
CC	34 (21.94)	55 (26.19)	1		33 (20.89)	43 (20.98)	1		31 (15.74)	65 (32.17)	1	
CT	80 (51.61)	93 (44.29)	1.37 (0.80-2.35)	0.210	88 (55.70)	110 (53.66)	1.04 (0.59-1.83)	0.888	101 (51.27)	99 (49.09)	2.16 (1.28-3.65)	0.004
TT	41 (26.45)	62 (29.52)	1.02 (0.56-1.86)	0.945	37 (23.41)	52 (25.37)	0.96 (0.50-1.84)	0.891	65 (32.99)	38 (18.81)	3.53 (1.49-8.33)	0.004
IL-1RN												
L/L	129 (83.22)	185 (88.10)	1		94 (59.49)	156 (76.10)	1		166 (84.26)	171 (84.66)	1	
2/L	26 (16.78)	25 (11.90)	1.50 (0.80-2.79)	0.206	64 (40.50)	49 (23.90)	2.11 (1.31-3.40)	0.002	31 (15.28)	31 (14.44)	1.03 (0.59-1.79)	0.924

[1]Adjusted for age, sex, smoking status and *Helicobacter pylori* infection. IL: Interleukin; OR: Odds ratio.

IL-1B-31, IL-1B-511 and IL-1RN polymorphisms and GC risk

The frequencies of genotypes *IL-1B*-31, *IL-1B*-511 and *IL-1RN* among the Tibet, Hui and Han ethnicities are summarized in Table 3. In the Tibet ethnicity group, the *IL-1B*-31 CC genotype was significantly more frequent in GC patients (32.90%) compared with controls (24.29%) (χ^2 = 4.98, P = 0.026). The risk of developing gastric cancer with this genotype was significantly increased (adjusted OR = 2.10, 95%CI: 1.09-4.04, P = 0.027).

In the Hui nationality group, the *IL-1RN* L/2 genotype was significantly more frequent in GC patients (40.50%) compared with controls (23.90%) (χ^2 = 11.47, P = 0.001). The risk of developing GC with this genotype was significantly increased (adjusted OR = 2.11, 95%CI: 1.31-3.40).

Unlike the results obtained for individuals belonging to either the Tibet or Hui populations, two genotype sites were associated with GC in the Han ethnicity. For the *IL-1B*-31 CT genotype, there was a significant difference between GC patients (51.77%) and controls (48.52%) (χ^2 = 4.61, P = 0.032). There was also a significant difference in the CC genotype between GC patients (27.92%) and controls (19.31) (χ^2 = 8.29, P = 0.004). The risk of developing GC in patients with *IL-1B*-31CT or CC genotypes was significantly increased (adjusted OR = 1.69, 2.29; 95%CI: 1.03-2.76, 1.28-4.10; P = 0.036, 0.005, respectively). In addition, for the *IL-1B*-511 genotypes, there was a statistically significant difference in the CT genotype distribution between GC patients (50.50%) and controls (49.09%) (χ^2 = 8.70, P = 0.003). Additionally, there was also a statistically significant difference in TT genotype distribution between GC patients (32.67%) and controls (18.81%) (χ^2 = 18.90, P = 0.000). The risk of developing GC in patients with the *IL-1B*-511 CT or TT genotypes was significantly increased (adjusted OR = 2.16, 3.53; 95%CI: 1.28-3.65, 1.49-8.33; P = 0.004, 0.004, respectively).

IL-1B-31, IL-1B-511 and IL-1RN polymorphisms and intestinal type GC risk

The identification of a genetic risk outline for GC could help the populations most at risk. Therefore, the prevalence of *IL-1B*-31, *IL-1B*-511 and *IL-1RN* polymorphisms in different GC subtypes were analyzed. In this study, there were 109, 106 and 139 cases (70.32%, 67.09% and 70.56%) of intestinal-type GC, and 46, 52 and 58 cases (29.68%, 32.91% and 29.44%) of diffuse or mixed-type GC in the Tibet, Hui and Han ethnicities, respectively. The frequencies of genotypes *IL-1B*-31, -511, and *IL-1RN* among intestinal-type GC and diffuse or mixed-type GC in all three populations are summarized in Table 4.

For individuals belonging to the Tibet ethnicity group, the *IL-1B*-31 CC genotype was only associated with intestinal type GC (P = 0.037) with an adjusted OR of 2.17 (95%CI: 1.05-4.51).

In the Hui ethnicity group, the *IL-1RN* 2 genotype was associated with both intestinal and diffuse types of GC (P = 0.007, 0.016, respectively) with adjusted ORs of 2.08 and 2.31 (95%CI: 1.22-3.56, 1.17-4.56, respectively).

In the Han ethnicity group, the *IL-1B*-31 CC genotype was only associated with intestinal type GC (P = 0.005) with an adjusted OR of 2.51 (95%CI: 1.32-4.76). However, compared to the TT genotype, the GC risk in *IL-1B*-31 CT carriers did not achieve the threshold of statistical significance (P = 0.067) with an adjusted OR of 1.68 (95%CI: 0.97-2.90). Moreover, both the *IL-1B*-511 CT and TT genotypes were only associated with intestinal type GC (P = 0.002, 0.000) with adjusted ORs of 2.74 and 5.66 (95%CI: 1.44-5.22, 2.82-11.33, respectively).

No other significant associations were found when GC patients were sorted according to age, sex, and presence of *H. pylori* infection (data not shown).

DISCUSSION

Like many other malignancies, GC develops as a result of complex interactions between environmental risk factors (e.g., unhealthy lifestyle, smoking, uncontrolled over-drinking, unhealthy diet, and *H. pylori* infection) and genetic alterations[15]. This gene-environment interaction can alter gene expression and promote cell growth and carcinogenesis. The *IL-1B* and *IL-1RN* polymorphisms

Table 4 Genotype distributions of the interleukin-1B-31, interleukin-1B-511 and *interleukin-1RN* polymorphisms among different subtypes of gastric cancer in patients from the Tibet, Hui and Han ethnicities *n* (%)

Genetype	Tibet							Hui							Han						
		Intestinal cases			Diffuse cases				Intestinal cases			Diffuse cases				Intestinal cases			Diffuse cases		
	Controls	Cases	OR (95%CI)[1]	*P* value	Cases	OR (95%CI)[1]	*P* value	Controls	Cases	OR (95%CI)[1]	*P* value	Cases	OR (95%CI)[1]	*P* value	Controls	Cases	OR (95%CI)[1]	*P* value	Cases	OR (95%CI)[1]	*P* value
IL-1B-31																					
TT	47 (22.38)	16 (14.68)	1		7 (15.22)	1		59 (28.78)	33 (32.29)	1		13 (25.00)	1		65 (32.18)	28 (20.14)	1		12 (20.69)	1	
CT	112 (53.33)	56 (51.38)	1.46 (0.75-2.84)	0.271	25 (54.35)	1.48 (0.59-3.70)	0.407	105 (51.22)	51 (48.11)	0.87 (0.49-1.54)	0.618	28 (53.85)	1.11 (0.51-2.39)	0.792	98 (48.52)	70 (50.36)	1.68 (0.97-2.90)	0.067	32 (55.17)	2.00 (0.82-4.88)	0.126
CC	51 (24.29)	37 (33.94)	2.17 (1.05-4.51)	0.037	14 (30.43)	1.86 (0.68-5.09)	0.228	41 (20.00)	22 (21.28)	0.93 (0.46-1.90)	0.845	11 (21.15)	1.18 (0.46-3.01)	0.734	39 (19.31)	41 (29.50)	2.51 (1.32-4.76)	0.005	14 (24.14)	1.79 (0.85-3.77)	0.126
IL-1B-511																					
CC	55 (26.19)	22 (20.18)	1		12 (25.53)	1		43 (20.98)	23 (21.70)	1		10 (19.23)	1		65 (32.17)	16 (11.51)	1		15 (25.86)	1	
CT	93 (44.29)	54 (49.54)	1.48 (0.76-2.60)	0.277	26 (55.32)	1.28 (0.59-2.79)	0.535	110 (53.66)	58 (54.72)	1.00 (0.53-1.89)	0.998	30 (57.69)	1.13 (0.48-2.62)	0.784	99 (49.09)	69 (49.64)	2.74 (1.44-5.22)	0.002	32 (55.17)	1.45 (0.72-2.93)	0.301
TT	62 (29.52)	33 (30.28)	1.25 (0.64-2.42)	0.518	9 (19.15)	0.62 (0.24-1.63)	0.336	52 (25.37)	25 (23.58)	0.91 (0.43-1.92)	0.811	12 (23.08)	0.92 (0.34-2.50)	0.872	38 (18.81)	54 (38.85)	5.66 (2.82-11.33)	0.000	11 (18.97)	1.23 (0.50-3.02)	0.645
IL-1RN																					
L/L	185 (88.10)	93 (83.22)	1		36 (84.78)	1		156 (76.10)	64 (60.38)	1		30 (57.69)	1		171 (84.66)	116 (83.45)	1		50 (86.21)	1	
2/L	25 (11.90)	16 (14.68)	1.32 (0.66-2.66)	0.439	10 (16.78)	1.87 (0.79-4.43)	0.158	49 (23.90)	42 (39.62)	2.08 (1.22-3.56)	0.007	22 (42.31)	2.31 (1.17-4.56)	0.016	31 (14.44)	23 (16.55)	1.09 (0.59-1.97)	0.807	8 (13.79)	1.02 (0.43-2.39)	0.971

[1]Adjusted for age, sex, smoking status and *Helicobacter pylori* infection. IL: Interleukin; OR: Odds ratio.

are implicated in cancer risk through their influences on *IL-1B* transcription.

Since El-Omar *et al*[5] reported that carriers of *IL-1B*-511 T or *IL-1B*-31 C were more susceptible to GC than other genotypes in 2000, other studies have reported on the associations between *IL-1B* and *IL-1RN* polymorphisms and GC risk in various populations but with mixed, or even conflicting results[6,7,10-14]. To date, at least four meta-analyses on the associations between *IL-1B* and *IL-1RN* polymorphisms and GC have been reported, however, their outcomes were different and even opposite[16-19]. In fact, the genetic/environmental interactions among different ethnic groups are quite complex. Thus, *IL-1B* and *IL-1RN* polymorphisms may play different roles in different populations or geographical areas.

Two studies have been performed to evaluate the differences in *IL-1B* and *IL-1RN* polymorphisms in patients of the same ethnicity - Chinese Han and Italian, respectively. Zeng *et al*[10] found that the *IL-1B*-511 T/T genotype frequency was significantly higher in patients with GC than in control subjects (25.0% *vs* 12.5%, $\chi^2 = 6.7$, $P = 0.01$) in the low GC prevalence region (Guangdong), but was similar (23.0% *vs* 23.0%) in the high prevalence region (Shanxi). Perri *et al*[13] did not find any association between GC occurrence and either *IL-1B*-511T or *IL-1RN* polymorphism when dividing the subjects between geographic areas displaying high prevalence rates (the North) or low prevalence rates (the South) in Italy.

To the best of our knowledge, this is the first study to examine the associations between *IL-1* polymorphisms and GC risk among several ethnicities in one area at the same time. We examined these polymorphisms and their potential association with GC risk among the Tibet, Hui and Han ethnicities in the Qinghai area of China. We found associations between *IL-1B*-511, *IL-1B*-31 and *IL-1 RN* polymorphisms and GC risk among Tibet, Hui and Han ethnicities in the Qinghai area, which were not identical.

In the Tibet ethnicity group, the *IL-1B*-31 CC genotype was associated with GC. Additionally, our study showed that the *IL-1B*-31 CC genotype was only associated with intestinal type GC. Our results are consistent with those from several studies in Chinese and Caucasian populations, where *IL-1B*-31 CC polymorphisms were associated with an increased risk of GC[10,20,21]. However, these results are inconsistent with those from other studies in Asian and Caucasian populations[14,22,23].

In the Hui ethnicity group, the *IL-1RN*2 was associated with GC, and further study supported that the *IL-1RN*2 polymorphism was associated with both intestinal and diffuse types of GC. These findings were in agreement with those previously reported, including studies from Caucasian, Arab and Asian (including Chinese) populations[13,20,22,24]. However, our findings also differ from those reported in several other studies[14,25,26].

In the Han ethnicity group, the *IL-1B*-31 CT and CC genotypes and the *IL-1B*-511 CT and TT genotypes were associated with GC compared with the *IL-1B*-31 TT genotype

and the *IL-1B*-511 CC genotype, respectively. Moreover, the *IL-1B*-31 CC genotype was also only associated with intestinal type GC. Importantly, although *IL-1B*-31 CT carriers displayed a trend in risk, they did not achieve the threshold of statistical significance. The *IL-1B*-511 CT and TT genotypes were only associated with intestinal type GC, compared with the CC genotype. While this is the same in Caucasian and Chinese populations[11,18,27,28], it differs from the findings observed in South Korean and Japanese populations in Asia[10,20]. This study also revealed that *IL-1RN* polymorphisms were not associated with increased risk of GC in the Han ethnicity group, which is similar to that seen in Japanese and South Korean populations[20].

It is interesting and important that the *IL-1B*-31, *IL-1B*-511 and *IL-1RN* polymorphisms and GC risk among the three ethnicities examined were not identical. Other studies have drawn similar conclusions. We believe that the differences among the ethnicities are related to different inherited gene backgrounds. This is supported by other studies which showed differential genetic/environmental interactions in different ethnic groups resulting in altered gene expression and altered effects on cell growth and tumorigenesis[29]. The gene distributions of *IL-1B*-31, *IL-1B*-511 and *IL-1RN* among the Tibet, Hui and Han ethnicities in Qinghai were different. Despite this, they were at least somewhat related to other Asian populations. The *IL-1B*-31 TT genotype was less frequent in the Tibet population (22.38%) than in the Han population (32.18%). The *IL-1B*-511 TT genotype was more frequent in the Tibet population (29.52%) than in the Han population (18.81%). The *IL-1B*-511 TT genotype was significantly lower in the Hui population (20.98%) than in the Han population (32.17%). In addition, the *IL-1RN* L was significantly lower in the Hui (76.10%) population compared to both the Tibet population (88.10%) and the Han population (84.66%). Ethnic origin is a crucial determinant of the frequency of genetic markers in all populations. Our data may reflect the influence of past selective pressures on the genotypes of Tibet, Hui and Han ethnicities over a long period of time. Han, Tibet and Hui ethnicities have different origins. The Han population is the major ethnicity, while the Tibet and Hui ethnicities are considered to be minorities in the Qinghai province of China. The selected healthy controls of the Tibet ethnicity were living in the Hainan Tibet Ethnicity Autonomous prefecture in Qinghai province, which belongs to the Tibet Anduo area. Shi *et al*[30] studied more than 5000 male samples from 73 East Asian populations and reconstructed the phylogenetic geography of the D-M174 lineage. The suggested frequency of D-M174 in Tibet (41.31%) was close to Japan (35.08%) but different from the Han ethnicity (< 5%). Thus, the Tibet gene feature is more similar to the Han ethnicity, but also has its own characteristics. The Hui ethnicity migrated from Central Asia, Persia and the Arab world. Yao *et al*[31] analyzed M*, N* and R* mtDNAs and found that the western Eurasian specific haplogroup frequency in the Hui population was 6.7%, but no western Eurasian type was found in Han Chinese samples from the same place. Since both the Tibet and Hui ethnicities practice endogamy, they tend to be ethnically homogeneous. Therefore, we believe that the Tibet, Hui, and Han ethnicities in the Qinghai area of China have different origins leading to different associations between *IL-1B*-31, *IL-1B*-511 and *IL-1RN* polymorphisms and GC risk.

Our study has some limitations. First, we did not consider education, consumption of alcohol, fresh fruits, and vegetables in the controls which could influence GC risk. Second, the altitude at which healthy controls lived was not considered. In this study, all of the Tibet controls and most of the Tibet patients lived in the plateau above 2800 meters of one another. For the Hui and Han populations, all controls and most patients lived within 2200 meters of each other. Finally, different eating habits among the groups were not investigated.

In conclusion, the present study shows different associations between the *IL-1B*-31, *IL-1B*-511 and *IL-1RN* polymorphisms and GC among the Tibet, Hui and Han ethnicities in the Qinghai area of China. No significant association was observed when GC patients were sorted by age, sex and the presence of *H. pylori* infection.

COMMENTS

Background

Studies suggest that polymorphisms in interleukin (IL)-1B and IL-1RN are associated with a differential risk of developing gastric cancer. However, there does not seem to be a consensus regarding these polymorphisms, since in some populations the polymorphisms are associated with increased disease occurrence, whereas in other populations, they are associated with a protective effect.

Research frontiers

There is no consensus regarding the associations between IL-1B, IL-RN polymorphisms and gastric cancers in different areas or ethnicities. The authors investigated the associations between IL-1B and IL-1RN polymorphisms and gastric cancers among the Tibet, Hui and Han ethnicities in China.

Innovations and breakthroughs

The outcomes of previous studies on the associations between *IL-1B* and IL-1RN polymorphisms and gastric cancer were different and even opposite. The genetic/environmental interactions among different ethnic groups are quite complex. Thus, IL-1B and IL-1RN polymorphisms may play different roles in different populations or geographical areas. This study suggests that carriers of the *IL-1B*-31 CC genotype had an increased risk of intestinal type gastric cancer in the Tibet ethnicity, carriers of the *IL-1B* 2/L genotype had an increased risk of both intestinal and diffuse types of gastric cancer in the Hui ethnicity, while carriers of the *IL-1B*-31 CC, *IL-1B*-511 CT, TT genotypes have an increased risk of intestinal type gastric cancer in the Han population.

Applications

The study results suggest that *IL-1B* and *IL-RN* genotypes may differentially contribute to gastric cancer among the Tibet, Hui and Han nationalities in the Qinghai area of China, and that IL-1B and IL-1RN polymorphisms may play different roles in different populations or geographical areas.

Terminology

Single nucleotide polymorphisms (SNPs) are short polymorphisms in the human DNA. SNPs occur once in every 300 nucleotides on average and can act as biological markers. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene's function. SNPs can also be used to track the inheritance of disease genes within families.

Peer review

This is a good descriptive study in which authors investigated IL-1B and IL-1RN polymorphisms in Han, Tibetan and Hui ethnic populations in Qinghai Province of China and their associations with gastric cancer risk in these populations. The topic is interesting and of potential clinical implications.

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