RESEARCH ARTICLE

Association of Cytokine Gene Polymorphisms with Gastritis in a Kazakh Population

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Abstract

Background: Gastritis and gastric cancer are the most common diseases in the Kazakh population. Polymorphisms in genes coding of cytokines have been played important role with gastric disease risk. The risk alleles of cytokines in patients with gastritis can predict the risk of developing gastric cancer. The aim of this study was to investigate cytokine gene polymorphisms as risk factors for the development of gastritis in a case-control study with gastritis patients and healthy individuals from the Kazakh ethnic group, living in North Kazakhstan. Materials and Methods: The polymerase chain reaction followed by direct sequencing were used for detection of two functional polymorphisms in the IL1 gene family, and TaqMan SNP Genotyping Assay Sets were applied for three potentially functional polymorphisms in the IL10 gene, and one in the TNFA promoter. Results: Association analysis of studied allelic variants and the development of gastritis in *H. pylori*-positive patients showed that IL1B -31C/C, IL1B -511T/T and IL1RN -2/2 allelic variants were associated with development of gastritis (OR=1.8 (1.07-3.16), p=0.025; OR=1.7 (1.04-2.99), p=0.035, and OR=4.92 (2.45-9.85), p<0.001) respectively. Haplotype C-T that combines both homozygous allelic variants of IL1B gene also had a statistically significant association with slightly higher OR (OR: 1.43, 95% CI: 1.08-1.88). Conclusions: The data from the current study showed that the genotype IL-1B -511T/-31C-IL1-RN-2 and *H. pylori* infection increase risk of gastritis in the Kazakh population. That genotype combination might be a factor increasing the risk of developing gastric cancer.

Keywords: *Helicobacter pylori* - gastritis - gastric cancer - polymorphism - cytokine

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Introduction

Gastric cancer is the second most common cause of mortality in the world. Gastric inflammation plays crucial roles in the developing of the gastric disease such as gastritis and gastric cancer. Gastritis is an inflammation of the mucous membrane of the stomach, accompanied by degenerative changes. Gastritis is exacerbated by the aberrations in the nutritional status, by spicy and high-fat foods, smoking, stress and the abuse of alcohol. During the inflammation, gastric mucosa becomes thinner and the number of fundic glands is reduced. In addition, infection of stomach with *Helicobacter pylori* may lead to undesirable consequences.

According to the recent studies, infection with *H. pylori* is a risk factor for the development of gastric cancer (Gehmert et al., 2009). Results from other study indicated that except infection *H. pylori* serum Zink level from antioxidant also might be indicator for damage gastric membrane and decreasing serum Zink level in patients with gastritis increasing the risk of gastric cancer (Zhang et al., 2012). From another study exists evidence that key factor in development of gastric cancer p53 gene intron alterations may contribute gastritis development and early detection of these alterations in precancerous lesions such as gastritis may be useful for prediction of risk developing of gastric cancer (Najjar Sadeghi et al., 2013). Gastric cancer is partly a hereditary disease and according recently study the infection *Helicobacter pylori* and the stomach lesions such as dysplasia, atrophy and chronic gastritis have been met more frequently in individuals with a family history of gastric cancer (Mansour-Ghanaei et al., 2012). In most cases the infection *Helicobacter pylori* is asymptomatic. *H. pylori* infectivity is highly dependent on ethnicity and geographical region (Gehmert et al., 2009; Martinez-Carrillo et al., 2010).

About 2/3 of the world population, including 25% of population in developed countries, are infected with *H. pylori*. This is due to the widespread use of antibiotics that promotes the spread of antibiotic resistance. In post-

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Soviet countries, the infection reaches 60-70%. Although the majority of infected people don't have symptoms of stomach diseases, persistent colonization and chronic inflammation increase the risk of gastritis (Gehmert et al., 2009; Martinez-Carrillo et al., 2010).

H. pylori infection induces the production of a cytokines in the lining of the stomach. The most frequently studied inflammatory-related genes with gastric disease are interleukin family genes such as IL1B, IL1RN, IL10, and tumor necrosis factor-alpha (TNFA), coding for the proteins IL-1β, IL-1ra, IL-10 and TNF-α, respectively. These cytokines play important role in definition of etiology of gastric diseases. Several studies have shown that the level of IL1B expression can be affected by two allelic variants at positions -511 (T/T, rs16944) and -31 (C/C, rs1143627) in the promoter region of the gene. These allelic variants are associated with increased transcription of IL1B. Interleukin 1 beta is a potent inhibitor of gastric acid secretion (Uno et al., 2002). Reduced acidity in the stomach leads to inhomogeneous resettlement of *H. pylori* from the pylorus to the body of the stomach. Therefore, these polymorphisms can be considered as a potential genetic factor in predisposition to gastritis, which determines the risk of malignant transformation.

A number of studies have demonstrated that the alleles -511T and -31C in IL1B gene are associated with high level of cytokines and severe inflammation of the stomach (Kato et al., 2001; Sierra et al., 2008). The anti-inflammatory cytokine IL1 receptor antagonist (IL1RN) contains a variable number of 86-bp tandem repeats and 5 different alleles have been detected in intron 2. The allele 2 has been associated with increased risk of gastric cancer in several studies (El-Omar et al., 2000). IL10 down-regulates cytotoxic response and polymorphisms of IL10 also associated with gastric cancer risk (Kim et al., 2014). Three polymorphisms in the IL10 promoter, such as IL-10-G1082A (rs1800896), -C819T (rs1800871), and C592A (rs1800872), are shown inflammatory response at the transcriptional level (Bidwell et al., 1999). The promoter polymorphism of TNFA-308 play important role in H. pylori-induced gastritis and also has been found to influence the risk of gastric cancer (Bhayal et al., 2013). The current theory describing the risk of atrophic gastritis caused by *H. pylori* infection does not always work in studies performed in different ethnic groups and geographic regions (Santtila et al., 1998; Figueiredo et al., 2002; Peek and Blaser, 2002; Hsu et al., 2004; Garza-Gonzalez et al., 2005; Perez-Perez et al., 2005; Al-Moundhri et al., 2006; Moorchung et al., 2007).

Thus, inflammation is dependent on ethnic and geographical difference that partially explains inconsistent results regarding association between the risk of gastric cancer and *H. pylori* infection. Although gastritis and gastric cancer is at the top of the list of most common diseases in the Kazakh population, the genetic basis for interindividual variations in the inflammatory response and cytokine production in the context of *H. pylori* infection, have not been studied for Kazakhstan.

The aim of this study was to investigate the association of cytokine gene polymorphisms with an increased risk of gastritis in H. pylori-positive groups in Kazakhs.

Materials and Methods

Patients

Five hundreds forty seven individuals participated in the case-control study, including 301 gastritis patients recruited at the National Scientific Medical Center (Astana). The participants' age was between of 13 and 80 years (mean age 42.3±15.2) and the male to female ratio was 130/171. The control group included 246 people, aged 18 to 74 years (mean age 37.6±14.2 male/female ratio=154/92), with no medical history of stomach diseases. Prior to the study, ethical approval was received from the Ethics Committee of the National Center for Biotechnology. The Ethics Committee approved the informed consent form and questionnaire form designed specifically for the study. Biological material was taken with the informed consent signed by all donors. Both, the control group and the study group were recruited from the same geographical area (North Kazakhstan region). Biopsy samples were taken during a routine fibrogastroscopy. *H. pylori* infection status was determined by imprint gastric cytology using Romanovsky-Giemsa stain.

DNA exstraction

Extraction of genomic DNA from clinical samples was performed by standard procedures from tissue.

PCR amplification, VNTR analysis and polymorphisms analysis using direct sequencing

All samples were genotyped for the VNTR of IL1RN, IL1 gene, IL10 and TNFA by polymerase chain reaction (PCR) and gel electrophoresis. IL1RN variations were determined using primers described by Tarlow et al. (Tarlow et al., 1993). The PCR conditions were as follows: 95°C for 4 min; then 30 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 40 s; then 72°C for 5 min. The obtaining amplicons were analyzed by gel electrophoresis. The alleles 1,2,3,4 and 5 were represent as described by Tarlow et al. (Tarlow et al., 1993), 4,2,5,3 and 6 86 bp repeats, respectively. The alleles 1 and 2, also named as long and short, respectively, represent the majority of alleles.

For genotyping IL10 and TNFA polymorphisms was used TaqMan SNP Genotyping Assay Sets and detection was performed according the protocol of manufacturer.

IL1B genotyping was performed by PCR using the following primers: (IL511 (rs16944) F 5'-ctgcataccgtatgttctctgcc-3', IL511R 5'-ggaatcttcccacttacagatgg-3', IL31 (rs1143627) F 5'-tcttttccccttccctttaact-3' and IL31R 5'-agagactcccttagcacctagt-3'). Amplification was performed under the following conditions: 95°C for 5 min; then 35 cycles of 95°C for 40 s, 58°C for 1 min; then 720C for 1 min by using Tetrad 2 thermal cycler (Bio-Rad Laboratories, USA).

PCR products were sequenced on ABI 3730xl automatic genetic analyzer (Applied Biosystems, USA). The obtained data were analyzed with SeqScape v 2.6 software (Applied Biosystems, USA).

Statistical analysis

The test for Hardy-Weinberg equilibrium was

performed using Web program (http://www.oege.org/software/hwe-mr-calc.shtml) of genotype frequencies in the selected allelic variants. Odds ratios (OR) were calculated by using the formula adjusted for small sample size (OR=ad/bc). Confidence interval (CI) at 95% significance level was also calculated. All calculations were performed using DeFinetti online tool (Institute of Human Genetics, Germany, http://ihg.gsf.de/cgi-bin/hw/hwa1.pl).

Results

A total of 547 individuals participated in the study, including 301 patients with gastritis and 246 healthy individuals. Allelic variants the genes of cytokines were determined by direct sequencing.

The allele frequencies, genotype frequencies and statistics summary of association analysis the genes of cytokines are shown in Table 1. There was not found statistically significant association of genotype frequencies from Hardy-Weinberg equilibrium (p=0.05) in IL1B -31C position between patients with negative *H. pylori* status and a control group. Here the IL1B -31CC had higher p=0.17 in order to fix significant association. Statistically significant differences in genotype frequencies of polymorphic loci IL1B -511 (C>T) between patients with negative *H. pylori* status and a control group were not identified. However the association analysis of the selected allelic variants with the development of gastritis in H. pylori-positive patients showed that IL1B -31C/C and IL1B -511T/T were associated with the development of gastritis (OR=1.8 (1.07-3.16), p=0.025 and OR=1.7 (1.04-2.99), p=0.035, respectively (Table 1). Overall, we describe seven genetic variations in the IL1 gene family, IL10, and TNFA gene. The IL1RN VNTR consists of five major alleles in possible genotypes. In our study 108 (59.0%) of the patients were carrying the most common genotypes L/L (108/183). The heterozygotes (2/L) and homozygotes (2/2) genotypes of the IL1RN gene were shown significant association with gastritis (OR=1.91, p=0.01, OR=3.89, p<0.001, respectively) and gastritis with infection *H. pylori* (OR=1.75, p=0.05, OR=4.92, p<0.001, respectively) (Table 1). The other genotypes of IL10 and TNFA genes were not shown significant association with gastritis in Kazakh population. The genotype distribution is shown in Table 1.

Haplotype C-T that combines both homozygous allelic variants also had a statistically significant association with slightly higher OR and statistical significance (OR: 1.43, 95%CI: 1.08-1.88) in H. pylori-positive patients with gastritis and the control group (Table 2).

Genotype frequencies in different ethnic groups are represented in the Table 3.

The frequency of IL1B-511T and IL1B-31C alleles was found to be variable in different ethnic groups (Table 3). The differences in two polymorphisms are statistically

Table 1. Genotype and Allele Distribution of Cytokines Polymorphisms from Patients with Gastritis

Genotype		Negative *H. pylori* Infection				Positive *H. pylori* Infection		
		Controls	Cases	OR(95%CI)	p value	Cases	OR(95%CI)	p value
IL1B-511	C/C	71 (28.9)	22 (25.9)	1		44 (20.4)	1	
	C/T	122 (49.6)	39 (45.9)	1.03 (0.56-1.87)	0.918	114 (52.8)	1.5 (0.95-2.37)	0.076
	T/T	53 (21.5)	24 (28.2)	1.46 (0.74-2.88)	0.272	58 (26.8)	1.7 (1.04-2.99)	0.035
	C	264 (53.6)	83 (48.8)	1		202 (46.8)	1	
	T	228 (46.34)	87 (51.2)	1.16 (0.66-2.03)	0.59	230 (53.2)	1.58 (1.03-2.44)	0.03
IL1B-31	T/T	71 (28.9)	22 (25.9)	1		46 (21.3)	1	
	C/T	129 (52.4)	40 (47.1)	1.0 (0.55-1.81)	0.998	115 (53.3)	1.3 (0.87-2.15)	0.162
	C/C	46 (18.7)	23 (27)	1.6 (0.80-3.22)	0.174	55 (25.4)	1.8 (1.07-3.16)	0.025
	T	271 (55.1)	84 (49.4)	1		207 (47.9)	1	
	C	221 (44.9)	86 (50.6)	1.16 (0.66-2.03)	0.59	225 (52.1)	1.5 (0.97-2.29)	0.06
IL1RN	L/L	161 (78.2)	108 (59.0)	1		83 (57.2)	1	
	2/L	32 (15.5)	41 (22.4)	1.91 (1.13-3.22)	0.01	29 (20.0)	1.75 (0.99-3.1)	0.05
	2/2	13 (6.3)	34 (18.6)	3.89 (1.96-7.72)	<0.001	33 (22.8)	4.92 (2.45-9.85)	<0.001
	L	354 (85.9)	257 (70.2)	1		195 (67.2)	1	
	2	58 (14.1)	109 (29.8)	2.48 (1.59-3.87)	<0.001	95 (32.8)	2.67 (1.67-4.26)	<0.001
IL10-1082	AA	133 (58.1)	108 (65.06)	1		73 (65.06)	1	
	GA	81 (36.2)	49 (29.52)	0.74 (0.50-1.10)	0.18	42 (29.52)	0.94 (0.61-1.44)	0.81
	GG	16 (5.7)	9 (5.42)	0.69 (0.32-1.50)	0.39	4 (5.42)	0.45 (0.15-1.32)	0.16
	A	347 (75.4)	265 (79.8)	1		188 (79)	1	
	G	113 (24.6)	67 (20.2)	0.73 (0.48-1.11)	0.14	50 (21)	0.86 (0.55-1.35)	0.52
IL10-819	TT	50 (21.8)	94 (12.5)	1		63 (12.5)	1	
	CT	113 (49.3)	98 (63.75)	0.46 (0.31-0.66)	0	69 (63.75)	0.48 (0.32-0.73)	0
	CC	66 (28.9)	41 (23.75)	0.33 (0.21-0.52)	0	26 (23.75)	0.31 (0.18-0.53)	0
	T	213 (46.5)	286 (61.4)	1		195 (61.7)	1	
	C	245 (53.5)	180 (38.6)	0.41 (0.27-0.62)	0.00002	121 (38.3)	0.42 (0.26-0.65)	0.00012
IL10-592	AA	57 (24.8)	62 (28.6)	1		47 (28.6)	1	
	AC	133 (57.8)	155 (71.4)	1.07(0.69-1.64)	0.75	114 (71.4)	1.04 (0.65-1.64)	0.86
	CC	40 (17.4)	0	0.01(0.00-0.18)	0	0	0.01 (0.00-0.25)	0
	A	247 (53.7)	279 (64.3)	1		208 (64.6)	1	
	C	213 (46.3)	155 (35.7)	0.82 (0.54-1.25)	0.36	114 (35.4)	0.79 (0.50-1.25)	0.33
TNFA-308	GG	143 (70.8)	183 (82.8)	1		115 (82.8)	1	
	GA	54 (26.7)	36 (16.3)	0.52 (0.32-0.84)	0.01	26 (16.3)	0.59 (0.35-1.01)	0.05
	AA	5 (2.5)	2 (0.9)	0.31 (0.06-1.63)	0.15	1 (0.9)	0.24 (0.02-2.15)	0.17
	G	340 (84.2)	402 (91)	1		256 (90.1)	1	
	A	64 (15.8)	40 (9)	0.50 (0.31-0.79)	0.003	28 (9.9)	0.56 (0.33-0.95)	0.03

Table 2. IL1B Haplotype Frequency

Patients with gastritis and control group							*H. pylori*-positive patients with gastritis			
-31	-511	the control group	all samples	the case group	OR (95%CI)	p value	all samples	the case group	OR (95%CI)	p value
T	T	0.033	0.022	0.013	0.40 (0.17-0.95)	0.038 protective	0.024	0.014	0.42 (0.16-1.10)	0.077
T	C	0.518	0.497	0.480	Reference haplotype	-	0.493	0.465	Reference haplotype	-
C	T	0.430	0.471	0.505	1.33 (1.38-1.72)	0.024 risk	0.472	0.518	1.43 (1.08-1.88)	0.01 risk
C	C	0.019	0.009	0.002	0.09 (0.01-0.71)	0.023 protective	0.011	0.002	0.13 (0.02-1.01)	0.052

*The frequency of the haplotype in Kazakhs

Table 3. IL1B -511T and IL1B -31C Allele Frequency in Different Ethnic Groups

Ethnic group	IL1B -511*T	p value (compared to Kazakhs)	IL-1B -31*C	p value (compared to Kazakhs)
Kazakhs (n=246)	228 (46.3)		221 (44.9)	
Caucasians[a] (n=299)	200 (34.6)	<0.001	197 (34.8)	<0.001
Chinese[b] (n=508)	454 (44.7)	0.544	514 (50.6)	0.038
African-Americans[a] (n=294)	311 (53.4)	0.020	335 (59.0)	<0.001

[a](Zabaleta et al., 2008); [b](He et al., 2011)

significant between the three ethnic groups, the exception there is in IL1B -511T (p=0.544) between Kazakh and Chinese groups. The alleles IL1B-511T and IL1B-31C more identified in an African-Americans (53.4 and 59.0%, respectively) than in other groups. In Caucasians IL1B-511T and IL1B-31C (34.6 and 34.8%, respectively) were less than Kazakh group.

Discussion

The prevalence of gastritis in the studied geographic area of Kazakhstan is 18% per 100.000 people (www.medinfo.kz). This proportion is significantly lower comparing to 24% per 100.000 people in 2003 (www.medinfo.kz). Partially, it may be explained by earlier prognosis of the disease and timely treatment. However, there are several regional risk factors for the Kazakh population, such as high colonization with H. pylori, caused by traditional dietary habits. At the same time, the role of genetic differences as a risk factor for the development of gastritis has not previously been investigated in Kazakh ethnic group.

In the present study, the effects of allelic variants of the cytokines on the risk of gastritis in the population of ethnic Kazakhs were examined. In the populations of East Asia and Europe alleles of interleukin-1 beta are associated with an increased risk of atrophic gastritis and gastric cancer (El-Omar et al., 2000; Matsukura et al., 2003; Yamada et al., 2006). A meta-analysis study on the relationship of IL1B polymorphism with the development of precancerous conditions of the stomach was conducted by Peleteiro et al. (Peleteiro et al., 2010). In particular, there is a weak association of the development of gastric epithelial metaplasia in carriers of T allele at position IL1B-511 (OR=1.86) (Peleteiro et al., 2010). Previously, the association of IL1B-511T/-31C alleles and IL1RN*2 with the risk of gastric cancer has been shown in the European population by El-Omar et al. (El-Omar et al., 2000).

A cohort study on Japanese population has shown that allele IL1B-511T was associated with increased expression of IL1B in the gastric mucosa infected with *H. pylori* (Furuta et al., 2004). Similar experimental findings were made in the study of Chinese population, when the same genotype was associated with gastric atrophy and hypochlorhydria (Yang et al., 2004).

However, the association of gene polymorphism IL1B with the risk of gastric cancer was not found in the Korean population. Lee et al. have not confirmed an association between the polymorphism of IL1B-31 and increased risk of gastric cancer (Lee et al., 2003). Matsukara and colleagues reported that ethnic differences of IL1B gene polymorphism affect the risk of gastric atrophy. On the other hand, no association was found between the polymorphism of the IL1B and the risk of atrophic gastritis in the Thai and Vietnamese populations (Matsukura et al., 2003). There is a higher occurrence of IL1B-511T and IL1B-31C alleles in African-Americans comparing to European population (Zabaleta et al., 2008). Thus, it can be concluded that the relationship between genetic polymorphisms of interleukin-1-beta and inflammation response in the mucous membrane of the stomach is not universal in different ethnic groups.

Differences between ethnic groups can also be seen on a haplotype level. For example, a haplotype that combines both homozygous risk alleles occurs two times more often in the African-Americans than in the Europeans (Zabaleta et al., 2008). In another study, Jie Yang and colleagues conducted haplotype analysis that defined the IL1B-31T and -511C as risk alleles, while a synergistic effect between the two loci was not found (Yang et al., 2004).

The genetic studies conducted in Asia are scarce, what makes situation less clear. Ryu et al. reported that the polymorphism of IL1B -511 and -31 loci was not associated with *H. pylori* infection and risk of gastric cancer in the Korean population.

In our study, the experimental group based on a status of *H. pylori* infection leads to statistically significant associations of IL1B-511T/T allele (OR=1.7, p=0.035), IL1B-31C/C allele (OR=1.8, p=0.025), and combination of both alleles with the risk of gastritis.

The results of our study show a minor association of haplotype containing both risk allele T-T and C-C (p=0.038, 0.023, respectively) with the risk of gastritis

(OR=1.33, p=0.024). The differentiation of patients according to the status of *H. pylori* infection further increases the power of the association of the C-T haplotype (OR=1.43, 95%CI: 1.08-1.88, p=0.01).

This is not surprising, considering the fact that constant inflammatory response to *H. pylori* infection causes peptic ulcer disease or chronic gastritis. These conditions, in turn, are risk factors for development of adenocarcinoma of the stomach (El-Omar, 2001). At least 1% of H. pylori-positive gastritis patients will develop gastric cancer (Persson et al., 2011). This process generally depends on the intensity of inflammation and patient's genetic constitution.

A meta-analysis study conducted by Persson et al. indicated an increase in the overall risk of developing the disease in the Asian population in carriers of IL1B-31 T allele (Persson et al., 2011). It can be assumed that the increase of risk is associated with high *H. pylori* infectivity of Asian populations.

Genotypes of the IL10 have presented different results depends on ethnic group. The genotype IL-10-1082G/-819C/-592C was associated with gastric diseases in Asians, while IL-10-1082A/-81T/-592T was linked to gastric disease risk in Caucasians. The racial differences, number of patients enrolled them age, diagnosis, study design may contribute the differences in the results (Kang et al., 2009). Some recently meta-analysis have been shown that IL-10 -819TT genotype may be a protective factor for gastric cancer in Asians (Yu et al., 2013). Moreover study from China has been demonstrated that the IL-10-592 polymorphism is associated with protective effect in non-cardia gastric cancer (Pan et al., 2013). In the present study we did not find the significant association between IL-10 polymorphism and the risk of development gastritis.

TNFA produces the inflammatory response against infection and as IL1B inhibits gastric acid secretion (Garza-Gonzalez et al., 2005). In our study, we investigated the association between TNF-α-308 G/A polymorphism and risk to developing to gastritis in a *Helicobacter pylori* infected Kazakh population. Some case-controls studies have been shown the correlation between TNF-α polymorphism and the risk of gastric cancer. El-Omar et al. observed TNF-α-308 AA genotype which linked with an increased risk of non-cardia gastric carcinoma in Hp seropositive individuals (OR=2.6). Other case-control studies, which were conducted in East Asia did not find significant association between TNF-α-308 polymorphism and the risk of gastric cancer. Our results indicate that the TNF-α-308 polymorphism does not play important role in risk of development of gastritis in Hp positive Kazakh population. The different results of these studies may be explained by the geographical enigma, which include the genetic heterogeneity and vary gene-environment interactions in the development of gastric diseases in different populations (Zhu et al., 2014).

As a result, our study has shown that the development of gastritis in the Kazakh population is affected by a combination of genotype IL-1B -511T/-31C/IL-1RN*2 and *H. pylori* infection. It is quite possible, that combination of these factors increases the risk of developing gastric cancer in patients with gastritis.

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