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Frequency of *IL-1B* Gene Polymorphisms in Patients with Gastroesophageal Cancer in the Hakkari Region

Hakkari Bölgesinde Tanısı Konulan Gastro-Özofagus Kanserli Hastalarda *IL-1B* Gen Polimorfizmlerinin Sıklığı

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ABSTRACT

Objective: Gastric cancer is a complex malignant tumor associated with chronic inflammation.In the present study, we aimed to investigate the frequency of *interleukin 1B* (*IL-1B*) gene polymorphisms affecting gene expression in patients with gastroesophageal cancer (GC) diagnosed in the Hakkari region.

Methods: Blood samples of 17 patients with GC (group 1) and 59 healthy controls (group 2) were enrolled in the study. The single-nucleotide polymorphisms (SNPs) rs1143627 c.-118C>T, rs16944 c.-598C>T, and rs1143634 c.315C>T polymorphisms in the *IL-1B* gene were studied among groups via polymerase chain reaction and restriction fragment length polymorphism. Results were analyzed by descriptive statistics and the x^2 test. The association between SNPs and GC risk was evaluated by odd ratios (ORs) and 95% confidence intervals.

Results: The frequencies of the three genotypes in the SNP rs1143627, rs16944, and rs1143634 were similar between the groups, and C>T transition was not found to be significant [(p=0.69, OR: 1.16 95%, confidence interval (CI): 0.54-2.51; p= 0.16, OR: 0.58 95%, CI: 0.26-1.25; p=0.7, OR: 0.83 95%, CI: 0.32-2.11, respectively].

Conclusion: Our results did not reveal any significant association between *IL-1B* gene SNPs and gastroesophageal cancer in the Hakkari region.

Keywords: Gastro-esophageal cancer, *IL-1B* gene, restriction fragment length polymorphism, rs1143627, rs16944, rs1143634

ÖZ

Amaç: Mide kanseri kronik enflamasyonla ilişkili kompleks malign bir tümördür. Bu çalışmada Hakkari bölgesinde tanı konulan gastroözofageal kanser (GK) hastalarında gen ekspresyonunu etkileyen *interlökin 1B* (*IL-1B*) gen polimorfizmlerinin sıklığını araştırmayı amaçladık.

Yöntemler: Çalışmaya 17 GK hastası (grup 1) ve 59 sağlıklı kontrolün (grup 2) kan örnekleri alındı. *IL-1B* genindeki tek nükleotid polimorfizmleri (SNP) rs1143627 c.-118C>T, rs16944 c.-598C>T ve rs1143634 c.315C>T polimorfizmleri, polimeraz zincir reaksiyonu ve kısıtlama fragman uzunluğu yoluyla gruplar arasında polimorfizm incelenmiştir. Sonuçlar tanımlayıcı istatistikler ve x^2 testi ile analiz edildi. SNP'ler ile GC riski arasındaki ilişki olasılık oranları (OO) ve %95 güven aralıkları (GA) ile değerlendirildi.

Bulgular: SNP'deki rs1143627, rs16944 ve rs1143634 genotiplerinin frekansları gruplar arasında benzerdi ve C>T geçişi anlamlı bulunmadı [p=0,69, OO: 1,16 %95, GA: 0,54-2,51]; p=0,16, OO: 0,58 %95, GA: 0,26-1,25; p=0,7, OO: 0,83 %95, GA: 0,32-2,11].

Sonuç: Sonuçlarımız Hakkari Bölgesi'nde *IL-1B* gen SNP'leri ile gastroözofageal kanser arasında anlamlı bir ilişki ortaya koymadı.

Anahtar Sözcükler: Mide-özofagus kanseri, *IL-1B* geni, kısıtlama fragmanı uzunluğu polimorfizmi, rs1143627, rs16944, rs1143634

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INTRODUCTION

Gastroesophageal cancer (GC) is one of the most harmful cancers in the world, predominantly in specific geographies such as East Asia, South America, and Eastern Europe (1-3). The risk factors for GC include genetic susceptibility, insufficient high-fiber food consumption, a stationary lifestyle, and chronic exposure to inflammation and oxidative stress (4-7). In particular, the chronic inflammatory microenvironment is a crucial contributing factor to GCs (8,9). The prevalence of GC is high in the Hakkari region. Because cancer is a multifactorial chronic disease, we aimed to investigate polymorphisms affecting the expression of one of these genes, interleukin (IL)-1B, in patients and control samples obtained from this region.

The *IL-1B* gene, located on chromosome 2q14, is a powerful inflammatory biomarker and participates in a variety of cellular activities, including immune response to pathogens, cell proliferation, differentiation, and apoptosis (6). In addition, IL-1B is a potent inhibitor of gastric acid secretion (10,11-13). Recently, single-nucleotide polymorphisms (SNPs) or mutations in the *IL-1* gene have been proposed as a key factor in determining gastric tumor morphogenesis (10-14). Several studies have supported the association of increased IL-1B secretion with SNP polymorphisms in the promoter of the *IL-1B* gene (15,16). Interestingly, the transition between C and T alleles in thethree SNPs of the *IL-1B* gene promoter, including rs1143627, rs16944, and rs1143634, have been associated with IL-1B levels (4,5,16-20).

This study was designed to investigate the frequency of genotype distribution in the SNPs rs1143627, rs16944, and rs1143634 within the *IL-1B* gene in patients diagnosed with gastric cancer and controls living in the Hakkari region.

MATERIALS and METHODS

Patients and control subjects

A total of 17 patients diagnosed with GC aged between 31 and 88 years (5 females and 12 males) (group 1) and 59 healthy controls aged between 21 and 78 years (17 females and 42 males) living in the same region (group 2) were included in the current study. This study was approved by the Başkent University Ethics Committee (approval number: KA 18/354) and supported by the Başkent University Research Fund. The present study was conducted by following the principles of the Declaration of Helsinki. Participants were enrolled after verbal and written informed consent was obtained. Patients in group 1 who were diagnosed with GC via histopathological examination were eligible for this study. Healthy controls in group 2 who were cancer-free subjects and living in the same region were randomly selected, and subjects in this group with any signs and symptoms of digestive system diseases and other systemic disorders were excluded.

Genotyping

Genomic DNA was extracted from peripheral blood using a commercial genomic DNA extraction kit (Invitrogen®, USA). The SNPs rs1143627 c.-118C>T, rs16944 c.-598C>T, and rs1143634 c.315C>T (referencegenome NM_000576.2) polymorphisms in the *IL-1B* gene were analyzed using polymerase chain reaction (PCR) - restriction fragment-length polymorphism. The primer sequences are listed in Table 1. Thermal cycling consisted of several steps: starting with an initial denaturation step at 95 °C for 3 min, followed by 35 cycles at 95 °C for 30 seconds; 53 °C for 30 seconds (the SNP rs1143627 and rs1143634), 50 °C for 30 seconds (the SNP rs16944), 72 °C for 45 s, and a final step of 72 °C for 5 min. PCR products were digested with specific restriction enzymes (Table 2). Finally, the end products were electrophoresed on 3% agarose gel for determining genotypes.

Statistical Analysis

The SPSS software package version 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were applied to demographic characteristics. Quantitative results are shown as means ± standard deviation. The frequencies of the genotypes and alleles in the two groups were analyzed according to the Hardy-Weinberg equilibrium and compared using the x^2 test. $P<0.05$ was considered significant.

RESULTS

In the present study, 17 patients with GC (group 1) and 59 healthy subjects (group 2) were enrolled to analyze the functional polymorphisms of rs1143627 C>T, rs16944 C>T, and rs1143634 C>T in the promoter region of the *IL-1B* gene.

The mean age was 65.58±13.26 years in group 1 and 37.28±13.37 years in group 2.

The ratio of female (n)/male (n) was 5/12 in group 1 and 17/42 in group 2. There was no significant difference between groups (p=0.96).

In terms of SNP rs1143627 C>T, the frequencies of wild-type (CC), variant heterozygote (CT), and variant homozygote (TT) genotype was 23.5%, 58.8%, 17.6% in group 1, 35.6%, 42.4%, 22% in group 2, respectively (p=0.48) (Table 3). The total C allele frequency was 56.8% in group 1 and 52.9% in group 2, whereas the total T allele frequency was 43.2% in group 1 and 47.1% in group 2. However, there was not a statistically significant difference between the two groups (p=0.69, OR: 1.16, 95% CI: 0.54-2.51) (Table 3).

In addition, the frequencies of wild-type (CC), variant heterozygote (CT), and variant homozygote (TT) genotype in SNP rs16944 C>T were 29.4%, 52.9%, 17.6% in group 1, 22%, 40.7%, 37.3% in group 2, respectively (p=0.31) (Table 3). The total C allele frequency was

Table 1. Primer sequences of the investigated *IL-1B* gene polymorphisms

SNPs	Primer sequences	
	Forward (5'-3')	**Reverse (5'-3')**
rs1143627	GCACAACGATTGTCAGGAAA	GAGCAATGAAGATTGGCTGA
rs16944	GGTAACAGCACCTGGTCTTG	AAGGGCAAGGAGTAGCAAAC
rs1143634	ATGCTCAGGTGTCCTCCAAG	ATTAGCAAGCTGCCAGGAG

SNPs: Single nucleotide polymorphisms, IL-1B: Interleukin 1B.

55.9% in group 1 and 42.4% in group 2, whereas the total T allele frequency was 44.1% in group 1 and 57.6% in group 2 (p=0.16, OR: 0.58 95% CI: 0.26-1.25) (Table 3).

Finally, the frequencies of wild-type (CC), variant heterozygote (CT), and variant homozygote (TT) genotype in the SNP rs1143634 C>T were 58.8%, 41.2%, 0.0% in group 1, 54.2%, 44.1%, 1.7% in group 2, respectively (Table3). There was a predominance of homozygote genotype (CC) in all groups, without significant difference between groups (p=0.83) (Table 3). Total C allele frequency was 79.4% in group 1, 76.3% in group 2, and the total T allele frequency was 20.6% in group 1, and 23.7% in group 2 (p=0.7, OR: 0.83 95% CI: 0.32-2.11) (Table 3).

DISCUSSION

GC is a multi-factorial and complex malignant tumor with a low survival rate (6). In the pathophysiology of the disease, IL-1B-induced chronic inflammatory microenvironment is reported as a key element in tumorigenesis, vascular, and extracellular changes for tumor invasion (21-26). In addition, IL-1B exacerbates the inflammatory microenvironment via induction of COX-2 and iNOS production (27).

An increase in GC incidence is positively associated with increased life prospects. Dysregulation of the immune system in aging populations is a critical risk factor for cancer morphogenesis. Indeed, the accumulation of inflammatory cytokines and mediators in advanced age aggravates the dysplastic transformation of gastroesophageal cells (23,24).

In recent years, association studies of the SNPs of the *IL-1B* gene have been the focus in GC susceptibility (28-32). To the best of our knowledge, for the first time in the literature, we investigated the association between GC and the SNPs rs1143627 C>T, rs16944 C>T, and rs1143634 C>T in a sample from the Hakkari population.

Table 2. Product lengths, restriction enzymes, genotypes and restriction patterns of the *IL-1B* gene polymorphisms

SNPs	Amplicon length (base pairs)	Restriction enzyme	Genotype	Restriction pattern (base pairs)
rs1143627	332	AluI	CC	199, 133
			CT	133, 102, 97
			TT	102, 97
rs16944	489	AvaI	CC	334, 155
			CT	489, 334, 155
			TT	489
rs1143634	317	TaqI	CC	205, 112
			CT	317, 205, 112
			TT	317

SNPs: Single nucleotide polymorphisms, IL-1B: Interleukin 1B.

Table 3. Comparison of the genotypes and allele frequencies in the IL-1B polymorphisms between the healthy controls and gastroesophageal cancer group

SNPs			Group 1, (n=17)	Group 2, (n=59)	p-value*	OR, (95% CI)
rs1143627	Genotype	CC	4 (23.5%)	21 (35.6%)	0.48	
		CT	10 (58.8%)	25 (42.4%)		
		TT	3 (17.6%)	13 (22.0%)		
	Allele	C	18 (52.9%)	67 (56.8%)	0.69	1.16 (0.54-2.51)
		T	16 (47.1%)	51 (43.2%)		
rs16944	Genotype	CC	5 (29.4%)	13 (22.0%)	0.31	
		CT	9 (52.9%)	24 (40.7%)		
		TT	3 (17.6%)	22 (37.3%)		
	Allele	C	19 (55.9%)	50 (42.4%)	0.16	0.58 (0.26-1.25)
		T	15 (44.1%)	68 (57.6%)		
rs1143634	Genotype	CC	10 (58.8%)	32 (54.2%)	0.83	
		CT	7 (41.2%)	26 (44.1%)		
		TT	0 (0%)	1 (1.7%)		
	Allele	C	27 (79.4%)	90 (76.3%)	0.7	0.83 (0.32-2.11)
		T	7 (20.6%)	28 (23.7%)		

*The p-values were calculated using x^2 test. Group 1: Patients with gastroesophageal cancer, Group 2: Healthy controls, OR: Odds ratio, CI: Confidence interval, SNPs: Single nucleotide polymorphisms, IL-1B: Interleukin-1B.

First, we found a higher frequency of the heterozygote variant (CT) genotype in the SNP rs1143627 in group 1 although the difference was insignificant. In addition, total T allele frequency was induced in group 1 without any significant difference. The results of this study were comparable with those of other polymorphism studies (4,33-37). Yang et al. (38) found that the T allele in the SNP rs1143627 was correlated with induced GC in the Chinese population. Additionally, He et al. (39) determined that the homozygote genotype (TT) in the SNP rs1143627 contributes to GC morphogenesis in China. Qiu et al. reviewed the clinical notes of 52 patients with GC and 52 healthy controls. They found that the CT and TT genotype was significantly higher in patients with GC, and they pointed to a significant positive association between the T allele and GC susceptibility in the Hakka population (6). The results of this study demonstrated a discordant distribution of the genotype frequencies in other studies. Several studies have noted that the CC genotype is a crucial risk factor for GC in the Chinese, Hispanic, and Caucasian populations (5,32,40-42). For instance, Takagi et al. (43) suggested that the CC genotype in the SNP rs1143627 was significantly associated with GC development in the Japan population via increased inflammatory cytokines such as IL-1B and IL-8. Collectively, these different outcomes may have arisen from the allelic heterogeneity in different geographic regions.

Second, we analyzed the SNP rs16944 C>T between the groups and found that the frequency of the wild-type (CC) and heterozygote variant (CT) genotype was higher in group 1. The CT genotype was predominant in both the groups. Additionally, the total C allele frequency was higher in group 1 than in group 2. However, there were no significant differences between the groups in terms of genotype and allele distribution. In support of this, Yang et al. (44) determined a significant interaction between the C allele and GC risk in Asians. In addition, this association was found dominantly with Helicobacter pylori infection in China (20). Similar to this study, Kato et al. (36) reported the clinical notes of 699 patients with gastric cancer. The bottom line of their study was that the C allele did not provide an additional impact on GC in the Japan population (36). In contrast, TT homozygosity has been proven to be a significant determinant in gastroesophageal tumorigenesis via induced IL-1B secretion in the Caucasian, Chinese, and Japanese populations (5,15,38,43,45,46). Moreover, it has been emphasized that the impact of the T allele in the SNP rs16944 may be nebulous in the high-risk areas of China, unlike in the low-risk areas (5,40). Eventually, the global differences in allele distribution display why it is so difficult to determine the impacts of the C>T transition in GC.

CONCLUSION

Finally, we compared the rs1143634 C>T polymorphism within the *IL-1B* gene between groups and found that wild type (CC) was higher in group 1 without statistical significance between the two groups. The majority of the three genotypes were also the wild type (CC) in both groups. This means that the C>T transition is uncommon in the Hakkari population. In the study by Al-Moundhri et al. (33), there was no association between the T allele and GC. On the other hand, other previous studies pointed out that the heterozygote (CT) and homozygote (TT) variant genotypes were significantly linked to GC development (47,48). Furthermore, it has been postulated that the aforementioned variants were correlated with induced IL-1B production in the gastric mucosa (49).

The importance of this study is that the patient and control populations were selected from a very limited geographic area of Türkiye, Hakkari. The city is rather a low-populated region of a similar ethnic background, and consanguineous marriages are frequent. In summary, we observed a similar distribution of the three genotypes among the groups. As the study population comprised a limited number of patients, future large-scale controlled studies will be more promising to shed light on how *IL-1B* gene polymorphisms are distributed in gastric cancer patients.

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Ethics

Ethics Committee Approval: This study was approved by the Başkent University Ethics Committee (approval numner: KA 18/354).

Informed Consent: Participants were enrolled after verbal and written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş., Design: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş., Data Collection or Processing: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş., Analysis or Interpretation: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş., Literature Search: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş., Writing: D.Y., S.A-D., Y.K., G.Ü., Y.K.T., F.İ.Ş.

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REFERENCES

1. Forman D, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. Best Pract Res Clin Gastroenterol 2006; 20: 633-49.
2. Moradi MT, Hashtchian AR, Yari K. Helicobacter pylori cagA-positive strains: gastric cancer susceptibility. Biharean Biologist 2013; 7: 86-9.
3. Roukos DH. Current status and future perspectives in gastric cancer management. Cancer Treat Rev 2000; 26: 243-55.
4. Erzin Y, Koksal V, Altun S, Dobrucali A, Aslan M, Erdamar S, et al. Role of host interleukin 1beta gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms in clinical outcomes in Helicobacter pylori-positive Turkish patients with dyspepsia. J Gastroenterol 2008; 43: 705-10.
5. Zeng ZR, Hu PJ, Hu S, Pang RP, Chen MH, Ng M, et al. Association of interleukin 1B gene polymorphism and gastric cancers in high and low prevalence regions in China. Gut 2003; 52: 1684-9.
6. Qiu B, Zou HY, Yang YH, Lai CF. Interleukin-1B-31 gene polymorphism in Hakka gastric cancer patients in Guangdong, China. Genet Mol Res 2014; 13: 5873-9.
7. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008; 25: 2097-116.
8. Abbasian MH, Abbasi B, Ansarinejad N, Motevalizadeh Ardekani A, Samizadeh E, Gohari Moghaddam K, et al. Association of Interleukin-1 Gene Polymorphism with Risk of Gastric and Colorectal Cancers in an Iranian Population. Iran J Immunol 2018; 15: 321-8.

9. Stubljar D, Jeverica S, Jukic T, Skvarc M, Pintar T, Tepes B, et al. The influence of cytokine gene polymorphisms on the risk of developing gastric cancer in patients with Helicobacter pylori infection. Radiol Oncol 2015; 49: 256-64.
10. van der Ploeg AH, Kumpf O, Seelow E, Almanza LC, Schlag PM, Schumann RR, et al. The course of gastric cancer following surgery is associated with genetic variations of the interleukin-1 receptor antagonist and interleukin-1β. Gastric Cancer 2015; 18: 77-83.
11. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. The role of interleukin-1 polymorphisms in the pathogenesis of gastric cancer. Nature 2001; 412: 99.
12. El-Omar EM, Chow WH, Rabkin CS. Gastric cancer and H. pylori: Host genetics open the way. Gastroenterology 2001; 121: 1002-4.
13. Camargo MC, Mera R, Correa P, Peek RM Jr, Fontham ET, Goodman KJ, et al. Interleukin-1 beta and interleukin-1 receptor antagonist gene polymorphisms and gastric cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006; 15: 1674-87.
14. Taguchi A, Ohmiya N, Shirai K, Mabuchi N, Itoh A, Hirooka Y, et al. Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. Cancer Epidemiol. Biomarkers Prev 2005; 14: 2487-93.
15. Kamangar F, Limburg P, Taylor P, Dawsey S. Re: Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J Natl Cancer Inst 2003; 95: 760-1.
16. Luomala M, Lehtimäki T, Elovaara I, Wang X, Ukkonen M, Mattila K, et al. A study of interleukin-1 cluster genes in susceptibility to and severity of multiple sclerosis. J Neurol Sci 2001; 185: 123-7.
17. Hwang IR, Kodama T, Kikuchi S, Sakai K, Peterson LE, Graham DY, et al. Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in Helicobacter pylori infection. Gastroenterology 2002; 123: 1793-803.
18. Haukim N, Bidwell JL, Smith AJ, Keen LJ, Gallagher G, Kimberly R, et al. Cytokine gene polymorphism in human disease: on-line databases. Genes Immun 2002; 3: 313-30.
19. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002; 420: 860-7.
20. Chen B, Luo MX, Zhou X, Lv Y, Su GQ. Correlation Between Interleukin-1β-511 C/T Polymorphism and Gastric Cancer in Chinese Populations: A Meta-Analysis. Med Sci Monit 2016; 22: 1742-50.
21. Terzić J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010; 138: 2101-14.
22. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardiac gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 2003; 124: 1193-201.
23. Smyth MJ, Cretney E, Kershaw MH, Hayakawa Y. Cytokines in cancer immunity and immunotherapy. Immunol Rev 2004; 202: 275-93.
24. Abdel-Latif MM, Duggan S, Reynolds JV, Kelleher D. Inflammation and esophageal carcinogenesis. Curr Opin Pharmacol 2009; 9: 396-404.
25. Lopetuso LR, Chowdhry S, Pizarro TT. Opposing Functions of Classic and Novel IL-1 Family Members in Gut Health and Disease. Front Immunol 2013; 4: 181.
26. Tran LS, Chonwerawong M, Ferrero RL. Regulation and functions of inflammasome-mediated cytokines in Helicobacter pylori infection. Microbes Infect 2017; 19: 449-58.
27. Lakhanpal M, Yadav DS, Devi TR, Singh LC, Singh KJ, Latha SP, et al. Association of interleukin-1β -511 C/T polymorphism with tobacco-associated cancer in northeast India: a study on oral and gastric cancer. Cancer Genet 2014; 207: 1-11.
28. Srivastava R, Kashyap A, Kumar M, Nath G, Jain AK. Mucosal IgA & IL-1β in Helicobacter pylori Infection. Indian J Clin Biochem 2013; 28: 19-23.
29. Shields PG, Haris CC. Cancer risk and low-penetrance susceptibility genes in gene-environment interactions. J Clin Oncol 2000; 18: 2309-15.
30. Erichsen HC, Chanock SJ. SNPs in cancer research and treatment. Br J Cancer 2004; 90: 747-51.
31. Gonzales CA, Sala N, Capella G. Genetic susceptibility and gastric cancer risk. Int J Cancer 2004; 100: 249-60.
32. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Interleukin- 1 polymorphism associated with increased risk of gastric cancer. Nature 2001; 412: 99).
33. Al-Moundhri MS, Al-Nabhani M, Al-Bahrani B, Burney IA, Al-Madhani A, Ganguly SS, et al. Interleukin-1beta gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer risk in an Omani Arab population. Gastric Cancer 2006; 9: 284-90.
34. Lee SG, Kim B, Choi W, Lee I, Choi J, Song K. Lack of association between pro-inflammatory genotypes of the interleukin-1 (IL-1B -31 C/+ and IL-1RN *2/*2) and gastric cancer/duodenal ulcer in Korean population. Cytokine 2003; 21: 167-71.
35. Wu MS, Wu CY, Chen CJ, Lin MT, Shun CT, Lin JT. Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese. Int J Cancer 2003; 104: 617-23.
36. Kato S, Onda M, Yamada S, Matsuda N, Tokunaga A, Matsukura N. Association of the interleukin-1 beta genetic polymorphism and gastric cancer risk in Japanese. J Gastroenterol 2001; 36: 696-9.
37. Murphy G, Thornton J, McManus R, Swan N, Ryan B, Hughes DJ, et al. Association of gastric disease with polymorphisms in the inflammatory-related genes IL-1B, IL-1RN, IL-10, TNF, and TLR4. Eur J Gastroenterol Hepatol 2009; 21: 630-5.
38. Yang J, Hu Z, Xu Y, Shen J, Niu J, Hu X, et al. Interleukin-1B gene promoter variants are associated with an increased risk of gastric cancer in a Chinese population. Cancer Lett 2004; 215: 191-8.
39. He XM, Zhao JM, Jiang L, Fu BY. Interleukin-1B gene polymorphism and sequence determination of the preliminary study in gastric cancer patients. Cancer Prev Treat 2004; 11: 814-6.
40. Kim J, Kim Y, Lee KA. Ethnic differences in gastric cancer genetic susceptibility: allele flips of interleukin gene. World J Gastroenterol 2014; 20: 4558-65.
41. Garza-González E, Hold G, Pérez-Pérez GI, Bosques-Padilla FJ, Tijerina-Menchaca R, Maldonado-Garza HJ, et al. [Role of polymorphism of certain cytokines in gastric cancer in Mexico: preliminary results.] Rev Gastroenterol Mex 2003; 68: 107-12.
42. Pan SX, Yang XH, Lin ZN. Hakka population has gene polymorphism in Guangdong province. Toxicology 2005; 19: 241-2.
43. Takagi A, Deguchi R, Kobayashi K, Miwa T. Cytokine expressions and H. pylori-associated gastric mucosal lesion. Keio J Med 2002; 51(Suppl 2): 51-2.
44. Yang J, Hu Z, Xu Y, Shen J, Niu J, Hu X, et al. Interleukin-1B gene promoter variants are associated with an increased risk of gastric cancer in a Chinese population. Cancer Lett 2004; 215: 191-8.
45. Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, et al. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. Gastroenterology 2010; 121: 823-9.
46. Furuta T, Shirai N, Sugimoto M. Controversy in polymorphisms of interleukin-1beta in gastric cancer risks. J Gastroenterol 2004; 39: 501-3.

47. Wen YY, Pan XF, Loh M, Yang SJ, Xie Y, Tian Z, et al. Association of the IL-1B +3954 C/T polymorphism with the risk of gastric cancer in a population in Western China. Eur J Cancer Prev 2014; 3: 35-42.
48. Ismaili A, Yari K, Moradi MT, Sohrabi M, Kahrizi D, Kazemi E, et al. IL-1B (C+3954T) gene polymorphism and susceptibility to gastric cancer in the Iranian population. Asian Pac J Cancer Prev 2015; 16: 841-4.
49. Jatoi A, Nguyen PL, Foster N, Sun D, Stella PJ, Campbell M, et al. Interleukin-1 genetic polymorphisms and their relationship to the cancer anorexia/weight loss syndrome in metastatic gastric and gastroesophageal junction adenocarcinoma. J Support Oncol 2007; 5: 41-6.