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STUDYING THE ROLE OF THE IL1β (T31C) CYTOKINE GENE ALLELIC POLYMORPHISM IN THE MECHANISMS OF FORMATION OF GASTRIC AND DUODENAL ULCER

Tursunova Minavvar Ulugbekovna1,
Salaeva Muborak Saidobdullaevna2,
Halimova Holida Hakimbaevna3,
Rustamov Makhmudjon4,
Musakov Mirzokhid Sabitdjanovich5,
Bobokulov Muhammad Fahriddinovich6
Uzbekistan, Tashkent, Tashkent Medical Academy
1 Assistant of the Department of Internal Medicine №2 and Endocrinology of Tashkent Medical Academy. Uzbekistan. Telefon: +998(91) 190 55 49. minavvar.tursunova@mail.ru
2 Candidate of medical sciences, Associate Professor of Internal Medicine №2 and Endocrinology of Tashkent Medical Academy. Uzbekistan. Telefon: +998(97) 711 70 98. Salaeva.66@mail.ru
3Holida Hakimbaevna Halimova, Assistant of the Department of Internal Diseases with Endocrinology №2 of the Tashkent Medical Academy, Kholida80kh@gmail.com
5Assistant of the Department of Hematology, transfusiology and laboratory work of the Tashkent Medical Academy, mirzokhid.musakov@mail.ru

Abstract

Purpose: To assess the nature of the distribution of allelic and genotypic variants of the polymorphic gene IL1β (T31C)

Material and methods: The study was conducted with the participation of 100 patients with GU and DU, aged 20 to 84 years, who were hospitalized at the multidisciplinary clinic of the Tashkent Medical Academy in the period from 2019-2021, as well as 85 healthy individuals without gastrointestinal diseases.

Results: We studied the features of the distribution of allelic and genotypic variants of the polymorphic cytokine gene IL1β (T31C) in groups of patients with DU and GU compared with healthy ones. The study made it possible to determine the participation of unfavorable C allele and T/C and C/C genotypes in the pathogenetic mechanisms of DU development.

Keywords: IL1β (T31C) cytokine gene polymorphism, alelle, genotype, gastric ulcer, duodenal ulcer.

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Introduction

Gastric ulcers of the digestive tract are characterized by lesions of the mucous membrane with spread to the submucosa or muscle tissue, which is often localized in the stomach or proximal part of duodenum [1]. The overall prevalence of gastric ulcer in the general population is 5-10% [2,3,4].

Damage to the mucous membrane of the stomach and duodenum is associated with a number of predisposing factors such as irregular nutrition, stressful situations, hypersecretion of hydrochloric acid in the gastric mucosa, H. pylori infection, tobacco use, alcohol, non-steroidal anti-inflammatory drugs (NSAIDs), etc. [5]. However, in the presence of all these factors, not all people develop gastric and duodenal ulcers, which emphasizes the presence of individual susceptibility to their development associated with the influence of polymorphic genes of a number of cytokines [5] In particular, the results of modern studies have shown the effect of the polymorphic gene interleukin 1β (IL1β), which regulates the production of interleukin 1β in the mucous membrane of the gastroduodenal tract, on an increased risk of formation of gastric and duodenal ulcers [7]. Meanwhile, there are conflicting views regarding the involvement of the IL1β gene in the pathogenetic mechanisms of the development of gastric and duodenal ulcers [6].

In this regard, the aim of the study was to assess the nature of the distribution of allelic and genotypic variants of the polymorphic IL1β gene (T31C) with the study of their role in increasing the risk of developing gastric ulcer (GU) and duodenal ulcer (DU) in Uzbekistan.

Material and Methods

The study was conducted with the participation of 100 patients with GU and DU (main group 1) aged 20 to 84 years (median age 42.7±2.3 years) who were hospitalized at the multidisciplinary clinic of the Tashkent Medical Academy (TMA) in the period from 2019-2021 years. Depending on the nosology, patients of the main group I were divided into two subgroups: Ia (n = 49) - patients with DU and Ib (n = 51) - patients with GU. The control group (group II) included 85 healthy individuals without a history of gastrointestinal tract diseases, corresponding to the main group of patients in terms of gender and age.

Molecular genetic analysis of the IL1β (T31C) gene polymorphism was carried out in the Laboratory of Molecular Genetics, Cytogenetics and FISH on the basis of the Republican Specialized Scientific and Practical Medical Center of Hematology (RSSPMCH, Republic of Uzbekistan, Tashkent). Isolation of the DNA molecule was carried out from peripheral blood using the AmpliPrime RIBO-prep kit (LLC Interlabservis, Russia). Detection of IL1β (T31C) gene polymorphism was carried out using test systems of LLC NPF Litekh (Russia). Amplification was carried out using a GeneAmp PCR-system 2720 thermal cycler (Applied Biosystems, USA). For statistical analysis, the package of statistical application programs "OpenEpi 2009, Version 2.3" was used.

Results and Discussion

The analysis of differences between the frequencies and frequencies of the genotypes of the IL1β (T31C) gene polymorphism is aimed at equalizing the Hardy-Weinberg (RHV, P>0.05) in the main ($\chi2$=2.34; P=0.128) and control groups ($\chi2$=0.48 ; P=0.465).) absence showed deviation.

Based on the analysis of the distribution of allelic and genotypic variants of the polymorphic IL1B gene (T31C) among the studied groups of patients (n=100) and healthy people (n=85), a number of features were found. Thus, in the healthy group, the carriage of the major and minor alleles T

and C was 84.1%/143 and 15.9%/27 cases, respectively. At the same time, the frequencies of the T/T, T/C, and C/C genotypes were 71.8%/61; 24.7%/21 and 3.5%/3 respectively.

Meanwhile, among patients of the main group, compared with healthy controls, the frequency of the main allele T decreased to 73.5%/147, while the minor allele C increased to 26.5%/53. Along with this, the main T/T genotype significantly decreased to 57.0%57 with an increase in the frequencies of the heterozygous T/C and homozygous mutant C/C genotypes to 33.0%/33 and 10.0%/10, respectively.

A similar picture was observed in the groups of patients with DU (Ia) and GU (Ib). In particular, among patients with DU, the frequency of the major C allele was the lowest among all the studied groups (66.3%/65), while the frequency of the minor T allele (33.7%/33) was opposite to the maximum. At the same time, regular dynamics was also observed in relation to genotypic frequencies, where the main T/T genotype was registered least of all (46.9%/23), and heterozygous T/C (36.7%/19) and homozygous mutant genotypes (14.3%/7) had their maximum frequency.

In the group of patients with GU, compared with healthy controls, the frequency of the major allele T decreased to 80.4%/82, while the frequency of the minor allele C increased to 19.6%/20. Along with this, the frequency of the main T/T genotype decreased to 66.7%/34, with an increase in the heterozygous T/C and homozygous for the minor allele C/C genotype to 27.4%/14 and 5.9%/3, respectively (Table 1).

Thus, an increase in the frequencies of minor unfavorable allele (C) and genotypes (T/C and C/C) of the IL1B (T31C) gene polymorphism among patients with gastric and duodenal ulcers may indicate their involvement in the pathogenetic mechanisms of their development.

Table 1 Analysis of the distribution of allele and genotype frequencies according to the IL1B (T31C) gene polymorphism in groups of patients with gastric and duodenal ulcers and healthy individuals

№	Group	alleles				genotypes					
		T		C		T/T		T/C		C/C	
		n	%	n	%	n	%	n	%	n	%
1	The main group of patients with DU , n=100	147	73.5	53	26.5	57	57.0	33	33.0	10	10.0
2	Ia – subgroup of patients with DU, n=49	65	66.3	33	33.7	23	46.9	19	38.7	7	14.3
3	Ib - subgroup of patients with GU, n=51	82	80.4	20	19.6	34	66.7	14	27.4	3	5.9
4	Control group, n=85	143	84.1	27	15.9	61	71.8	21	24.7	3	3.5

Assessing the statistical significance of the differences found in the distribution of allele and genotype frequencies for the polymorphic cytokine gene IL1B (T31C) in the main group of patients compared with the healthy group, a statistically significant increase in the frequency of the minor allele C by 1.9 times (26.5% vs. 15.9%; $\chi 2=6.1$; P=0.03; OR=1.9; 95%CI: 1.14-3.19). At the same time, despite the increase in the frequencies of heterozygous (T/C) and mutant (C/C) genotypes among the main group of patients compared with healthy ones by 1.5 times (33.0% vs. 24.7%; $\chi 2=1.5$; P=0.3; OR= 1.5; 95% CI: 0.79-2.86) and 3.0 times (10% vs. 3.5%; $\chi 2=2.9$; P=0.1; OR=3.0; 95% CI: 0.85-10.8) differences between the studied groups did not reach a statistically significant character. However, in relation to the mutant C/C genotype, there was a clear trend

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towards its increase among patients of the main group (Table 2). Therefore, the found statistically significant difference in the carriage of the unfavorable C allele (χ2=6.1; P=0.03) and the trend in the carriage of the mutant C/C genotype (χ2=2.9; P=0.1) in the main group of patients compared with healthy ones proves their participation in mechanisms of formation of peptic ulcer of the stomach and duodenum in Uzbekistan.

Table 2 Differences in the distribution of allele frequencies and genotypes of the IL1β (T31C) gene polymorphism among the main group of patients and healthy groups.

Alleles and genotypes	Number of alleles and genotypes in groups				χ^2	P	OR	95% CI
	Main		Control					
	N	%	n	%				
T	147	73.5	143	84.1	6.1	0.03	0.5	0.31 - 0.87
C	53	26.5	27	15.9	6.1	0.03	1.9	1.14 - 3.19
T/T	57	57.0	61	71.8	4.3	0.05	0.5	0.28 - 0.96
T/C	33	33.0	21	24.7	1.5	0.30	1.5	0.79 - 2.86
C/C	10	10.0	3	3.5	2.9	0.10	3.0	0.85 - 10.8

Comparing the distribution frequencies of allelic and genotypic variants of the polymorphic IL1B gene (T31C) in the group of patients with DU, a statistically highly significant increase in the frequency of the minor allele C by 2.7 times (33.7% vs. 15.9%; χ2=11.3; P=0.01; OR=2.7; 95 %CI: 1.51-4.78). At the same time, compared with healthy people, in terms of the frequency of the heterozygous T/C genotype among patients with DU, there was a clear trend towards its increase by 1.9 times (38.8% vs. 24.7%; χ2=2.9; P=0.1; OR=1.9; 95% CI: 0.91 - 4.09). Meanwhile, among patients with DU, compared with healthy patients, the frequency of the mutant C/C genotype increased statistically significantly by 4.6 times (14.3% vs. (Table 3).

Thus, the unfavorable minor allele C, the heterozygous T/C genotype, and the minor mutant C/C genotype of the polymorphic IL1B (T31C) gene increase the risk of developing DU by 2.7 (χ2=11.3; P=0.01), 1.9 (χ2=2.9; P= 0.1) and 4.6 times (χ2=5.2; P=0.03). Therefore, they can be considered as genetic factors involved in the pathogenetic mechanisms of the development of DU.

Table 3 Differences in the distribution of allele frequencies and genotypes of the IL1β (T31C) gene polymorphism among patients with DU and in the healthy group

Alleles and genotypes	Number of alleles and genotypes in groups				χ^2	P	OR	95% CI
	Subgroup Ia		Control					
	N	%	n	%				
T	65	66.3	143	84.1	11.3	0.01	0.4	0.21 - 0.66
C	33	33.7	27	15.9	11.3	0.01	2.7	1.51 - 4.78
T/T	23	46.9	61	71.8	8.2	0.01	0.3	0.17 - 0.72
T/C	19	38.8	21	24.7	2.9	0.10	1.9	0.91 - 4.09
C/C	7	14.3	3	3.5	5.2	0.03	4.6	1.24 - 16.76

A similar comparative analysis of the distribution frequencies of allelic and genotypic variants of the polymorphic IL1B (T31C) gene, carried out in the group of patients with GU compared with healthy people, revealed a statistically insignificant increase in the frequency of the minor allele C by 1.3 times (19.6% vs. 15.9%; χ2=0.6; P=0.5; OR=1.3; 95%CI: 0.68 - 2.44). In addition, in the group of patients with GU, the frequencies of heterozygous T/C and homozygous minor C/C

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genotype also statistically insignificantly increased compared with healthy ones in 1.2 (27.5% vs. 24.7%; χ2=0.1; P=0.8; OR=1.2; 95 %CI: 0.52 - 2.54) and 1.7 times (5.9% vs. 3.5%; χ2=0.4; P=0.6; OR=1.7; 95%CI: 0.34 - 8.65) (Table 4).

Thus, the absence of statistically significant differences in the distribution of frequencies of allelic and genotypic variants of the IL1B (T31C) polymorphic cytokine gene in the studied group of patients with GU compared with healthy ones indicates the absence of their participation in the pathogenetic mechanisms of GU development in Uzbekistan.

Table 4 Differences in the distribution of allele frequencies and genotypes of the IL1β (T31C) gene polymorphism among patients with GU and in the healthy group.

Alleles and genotypes	Number of alleles and genotypes in groups				χ^2	P	OR	95% CI
	Subgroup Ib		Control					
	N	%	n	%				
T	82	80.4	143	84.1	0.6	0.50	0.8	0.41 - 1.46
C	20	19.6	27	15.9	0.6	0.50	1.3	0.68 - 2.44
T/T	34	66.7	61	71.8	0.4	0.60	0.8	0.37 - 1.66
T/C	14	27.5	21	24.7	0.1	0.80	1.2	0.52 - 2.54
C/C	3	5.9	3	3.5	0.4	0.60	1.7	0.34 - 8.65

Comparative analysis of the results of the distribution of allelic and genotypic frequencies of the polymorphic cytokine gene IL1β (T31C) in the group of patients with DU compared with patients with PU showed statistically significant differences in the increase in the frequency of the minor allele C by 2.1 times (33.7% vs. 19.6%; χ2=5.1 ; P=0.03; OR=2.1; 95%CI: 1.1 - 3.94). However, in the carriage of heterozygous T/C (38.8% versus 27.5%; χ2=1.4; P=0.3; OR=1.7; 95% CI: 0.72–3.87) and homozygous mutant C/C (14.3% versus 5.9%; χ2=2.0 ; P=0.2; OR=2.7; 95% CI: 0.68 – 10.52) no statistically significant differences were found between genotypes.

Thus, the results of a comparative analysis of differences in the distribution of frequencies of alleles and genotypes of the polymorphic gene IL1B (T31C) between the groups of patients with DU and GU revealed a statistically significant difference in the carriage of the unfavorable C allele, which, compared with GU, statistically significantly increased the risk of developing DU by 2.1 times (χ2=5.1; P=0.03), which once again proves the role of the minor allele C in the pathogenetic mechanisms of the development of DU in Uzbekistan.

Conclusion

Thus, we studied the features of the distribution of allelic and genotypic variants of the polymorphic cytokine gene IL1B (T31C) in groups of patients with DU and GU compared with healthy ones. The study made it possible to detect the participation of unfavorable C allele and T/C and C/C genotypes in the pathogenetic mechanisms of DU development. In particular, it was determined that the unfavorable minor C allele, the heterozygous T/C genotype, and the minor C/C mutant genotype of the IL1B (T31C) polymorphic gene increase the risk of developing DU by 2.7 (χ2=11.3; P=0.01), 1.9 (χ2=2.9 ; P=0.1) and 4.6 times (χ2=5.2; P=0.03).

The results obtained allow us to consider them as genetic factors involved in the pathogenetic mechanisms of the development of DU.

REFERENCES

1. Burada F. Angelescu C., Ioana M., Mitrut P., Moraru E., Riza A. et al. IL-10-1082 A/G POLYMORPHISM AND RISK OF THE GASTRIC CANCER. Annals of RSCB. 2010;15(1):93-97. Vol.13 No.2 Spring 2018 IRANIAN JOURNAL OF PATHOLOGY.
2. Cheng H.H., Chang C.S., Wang H.J., Wang W.C. Interleukin-1beta and -10 polymorphisms influence erosive reflux esophagitis and gastritis in Taiwanese patients J Gastroenterol Hepatol, 25 (2010), pp. 1443-1451.
3. Kang J.M., Kim N., Lee D.H., Park J.H., Lee M.K., Kim J.S. et al. The effects of genetic polymorphisms of IL-6, IL-8, and IL-10 on Helicobacter pylori-induced gastroduodenal diseases in Korea J Clin Gastroenterol, 43 (2009), pp. . 420-428.
4. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and Treatment of Peptic Ulcer Disease. Am J Med. 2019 Apr;132(4):447-456. doi: 10.1016/j.amjmed.2018.12.009. Epub 2019 Jan 3. PMID: 30611829.
5. Lehours P, Ferrero RL. Review: Helicobacter: Inflammation, immunology, and vaccines. Helicobacter. 2019 Sep;24 Suppl 1:e12644. doi: 10.1111/hel.12644. PMID: 31486236.
6. Martínez-Campos, C., Torres-Poveda, K., Camorlinga-Ponce, M. et al. Polymorphisms in IL-10 and TGF-β gene promoter are associated with lower risk to gastric cancer in a Mexican population. BMC Cancer 19, 453 (2019). https://doi.org/10.1186/s12885-019-5627-z
7. Narayanan M, Reddy KM, Marsicano E. Peptic Ulcer Disease and Helicobacter pylori infection. Mo Med. 2018 May-Jun;115(3):219-224. PMID: 30228726; PMCID: PMC6140150.
8. Rad R., Dossumbekova A., Neu B., Lang R., Bauer S., Saur D. et al. Cytokine gene polymorphisms influence mucosal cytokine expression, gastric inflammation, and host specific colonisation during Helicobacter pylori infection. Gut. 2004;53(8):1082-9. https://doi.org/10.1136/gut.2003.029736 PMID:15247172 PMCID:PMC1774164.
9. Rezaeishahmirzadi M., Motamedi Rad N., Kalantar M., Ayatollahi H., Shakeri S., Sheikhi M., Shekari M. The Association of Gastritis and Peptic Ulcer With Polymorphisms in the Inflammatory-related Genes IL-4 and in Iranian Population Iran J Pathol.2018; 13(2): 229-236.
10. Seno H., Satoh K., Tsuji S., Shiratsuchi T., Harada Y., Hamajima N. et al. Novel interleukin-4 and interleukin-1 receptor antagonist gene variations associated with non-cardia gastric cancer in Japan: comprehensive analysis of 207 polymorphisms of 11 cytokine genes. J Gastroenterol Hepatol. 2007;22(5):729-37. https://doi.org/10.1111/j.1440-1746.2007.04934.x PMID:17444864.