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Value of the Polymorphism rs1800471 TGFB1 Gene in the Formation of a Predisposition to Duodenal Ulcer and Chronic Gastritis

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Abstract Conducted the detection of genetic polymorphism rs1800471 of TGFb1 gene in unrelated patients of Uzbek nationality with clinically and endoscopically established gastroduodenal diseases, including in patients with diagnosed complicated forms of duodenal ulcer (DU) and chronic gastritis (ChG). It is determined that the carriage of the heterozygous G/C genotype of the TGFb1 gene (rs1800471) is associated with a high risk of development of DU and ChG. It is also revealed that the homozygous genotype G/G possesses a protective anti-inflammatory role in the pathogenesis of ulcerative and inflammatory lesions of the gastric mucosa and duodenum. The burden of unfavorable homozygous genotype C/S in 1.7 and 6.5 times statistically increases the risk of development of DU and ChG, respectively. There were no statistically significant differences between DU and ChG.

Keywords Polymorphism rs1800471 of TGFb1 gene, Duodenal ulcer (DU), Chronic gastritis (ChG), Genotype, Protective

1. Introduction

As is known, the superfamily of the transforming growth factor TGF-β (transforming growth factor beta) refers to multifunctional peptides from the cytokine group that controls proliferation, differentiation, and other functions in many cell types. They play a fundamental role in the regulation of basic biological processes, such as growth, development, maintenance of tissue homeostasis and the functioning of the immune system. TGF-β is considered to be a cytokine of systemic action, since this peptide and its specific receptors have been identified in almost all cell types. [1, 2].

Among the known growth factors, cytokine TGF-β1 is considered the main mediator of fibrogenesis. [3, 4]. In addition to the function of the fibroblast inducer, it is currently recognized as a multifunctional cell growth factor. In particular, TGF-β1 inhibits cell growth by inhibition of the G1 phase of the cell cycle and stimulates apoptosis in various cells [5]. Increased expression of the TGF-β1 gene is associated with pathological conditions due to the processes of fibrosis and scarring [6].

TGF-β1 belongs to the group of anti-inflammatory cytokines that inhibits such inflammatory processes modulated by IL-1 and TNF-α, such as homing, cell adhesion, chemotaxis. TGF-β1 inhibits the proliferation of T and B-lymphocytes, inhibits the activity of macrophages and natural killers [7]. Normally, TGF-β1 regulates the growth of cells of the gastric mucosa, in particular the cells of the pit epithelium [10, 8]. TGF-β sequentially activating the proteins of apaptosis (Smad, Bim) and caspase 9, is involved in the physiological regeneration of the gastric mucosa.

Recent years in scientific literature discuss the role of polymorphism 915G> C (Arg/Pro, rs1800471) gene TGFB1 in the development of gastroduodenal diseases. However, the role of the genotypic variants of this gene in the formation and development of duodenal ulcer (DU) and chronic gastrit (ChG) has not been studied sufficiently.

2. Main Body

2.1. Purpose of the Study

Genomic typing of polymorphic region rs1800471 of TGFB1 gene in patients with gastroduodenal diseases and in relatively healthy donors of Uzbek nationality with the subsequent analysis of the possible association of this polymorphism with development of DU and ChG.

To study the frequency distribution of the genotypic

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variants of the polymorphism rs1800471 of the TGFB1 gene among patients with gastroduodenal diseases and to assess their role in the development and characteristics of the clinical course of DU and ChG.

2.2. Material and Methods of Investigation

Detection of genetic polymorphism rs1800471 of TGFb1 gene was performed in 148 unrelated patients of Uzbek nationality with clinically and endoscopically established gastroduodenal diseases, including 81 patients diagnosed with complicated forms of DU and in 67 patients with ChG. Patients with complicated forms of DU were hospitalized at the Republican Scientific Center for Emergency Medical Care, and those with ChG were in the 1st Clinic of the Tashkent Medical Academy.

The control group consisted of 139 healthy unrelated persons who had no history of gastrointestinal pathology of the Uzbek nationality, corresponding to the sex and age of the group of patients with gastroduodenal pathology ($p > 0.05$). All patients or their relatives, as well as individuals of the control group received informed consent to conducting research.

The polymorphism rs1800471 of the TGFB1 gene was tested on a programmable thermal cycler from Applied Biosystems, 2720 (USA), using the test systems of the company Liteh (Russia), according to the manufacturer's instructions.

Specificity and number of amplified fragments were checked by agarose gel electrophoresis (Figure 1).

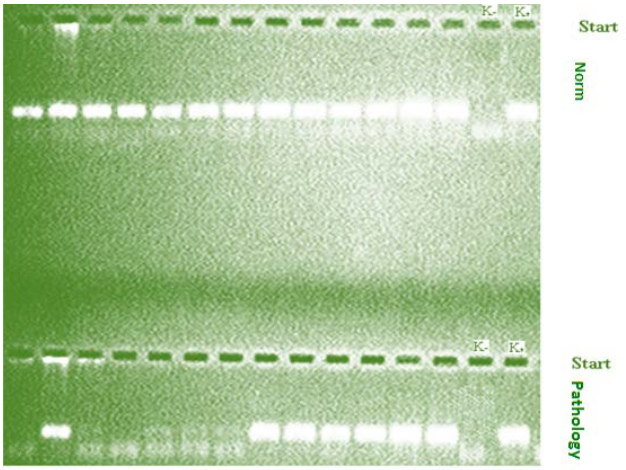

Figure 1. Electrophoregram of detection of rs1800471 polymorphism of TGFB1 gene

Statistical analysis of the results was carried out using the package of statistical programs "Open Epi 2009, Version 2.3".

2.3. Results and Discussion

In patients with gastroduodenal diseases, there is a significant increase in the proportion of carriers of the unfavorable Pro (C) allele from 11.5 to 19.9% ($\chi2 = 7.6$; $P = 0.006$; $OR = 1.9$; 95% CI 1.20-3.04). Approximately the same values ($x2 = 0.1$, $P = 0.7$, $OR = 0.9$, 95% CI 0.50-1.58) of the carrier of the Pro (C) allele were noted both in the subgroup of patients with DU (19.1%) and in subgroup of patients with ChG (20.9%), which also differ significantly ($\chi2 = 4.8$, $P = 0.03$, $OR = 1.8$, 95% CI 1.06-3.11 and $\chi2 = 6.4$, $P = 0.01$, $OR = 2.0$, 95% CI 1.16-3.54, respectively) from the similar parameter of the control group of healthy individuals (11.5%) (Figure 2 and Table 1), which indicates the association of this allele with an increased risk of gastroduodenal diseases.

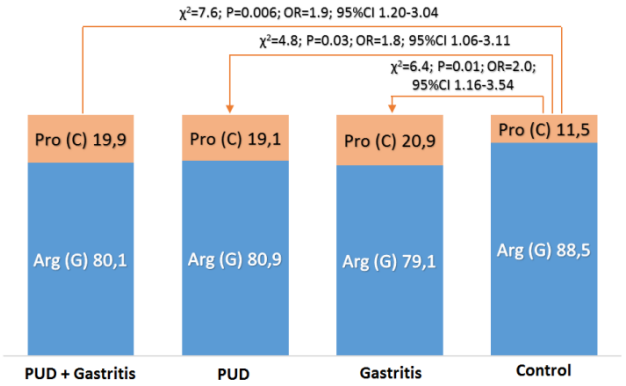

Figure 2. Frequency of alleles of polymorphism rs1800471 of TGFb1 gene in patients with gastroduodenal ptology and relatively healthy donors

Table 1. The frequency of genotypes of polymorphism rs1800471 of TGFb1 gene in patients with gastroduodenal pathology and relatively healthy donors

Group	Genotype		
	G/G	G/C	C/C
Basic	93	51	4
	*χ^2=7.5; P=0.06; OR=0.5; 95% CI 0.28-0.81; RR=0.81; CI 0.69-0.95	*χ^2=5.9; P=0.01; OR=1.9; 95% CI 1.12-3.23; RR=1.6; CI 1.08-2.35	*χ^2=1.6; P=0.2; OR=3.8; 95% CI 0.4-34.73; RR=3.8; CI 0.42-33.2
Duodenal ulcer (DU)	51	29	1
	*χ^2=5.5; P=0.02; OR=0.5; 95% CI 0.26-0.89; RR=0.8; CI 0.670-0.979	*χ^2=5.3; P=0.02; OR=2.0; 95% CI 1.10-3.72; RR=1.7; CI 1.07-2.55	*χ^2=0.1; P=0.7; OR=1.7; 95% CI 0.106-27.9; RR=1.7; CI 0.10-27.06
Chronic gastritis (ChG)	42	22	3
	*χ^2=5.1; P=0.02; OR=0.5; 95% CI 0.25-0.91; RR=0.8; CI 0.65-0.99	*χ^2=3.0; P=0.08; OR=1.8; 95% CI 0.92-3.40; RR=1.5; CI 0.954-2.42	*χ^2=3.3; P=0.07; OR=6.5; 95% CI 0.66-63.39; RR=6.2; CI 0.65-58.71
	**χ^2=0.002; P=0.9; OR=1.0; 95% CI 0.51-1.97; RR=1.0; CI 0.78-1.28	**χ^2=0.1; P=0.7; OR=1.0; 95% CI 0.57-2.25; RR=1.1; CI 0.69-1.71	**χ^2=1.5; P=0.2; OR=0.3; 95% CI 0.02-2.62; RR=0.3; CI 0.02-2.58
Control	108	30	1

Note:
* - statistical difference in comparison with the control group.
** - statistical difference in comparison with the subgroup of the DU

It should be noted that in both subgroups of patients, as well as in the control group of healthy individuals, carriers of all three variants of genotypes were present, including the rare C/C genotype. As a necessary consequence of the increase in the Pro-C (allele) carrier share in both subgroups of patients with gastroduodenal diseases, there is a significant decrease in G/G genotype carriers and a significant increase in detectability of the heterozygous genotype G/C and a slight increase in the homozygous C/C genotype (Table 1). It is known that the polymorphism of the gene of this cytokine at the +915 G/C locus affects the production of TGF-β1 as follows: the G/G genotype leads to high production, G/C to the intermediate and C/C to the low [10].

To the protective (anti-inflammatory) role of the homozygous genotype G/G in the pathogenesis of ulcerative and inflammatory lesions of the mucous membrane of the stomach and duodenum is indirectly indicated by a significant decrease in the proportion of carriers of this genotype in the combined group of patients with gastroduodenal pathology ($\chi2 = 7.5$; P = 0.06; OR = 0.5; 95% CI 0.28-0.81), as well as in patients with DU ($\chi2 = 5.5$, P = 0.02, OR = 0.5, 95% CI 0.26-0.89) and ChG ($\chi2 = 5.1$; P = 0.02; OR = 0.5; 95% CI 0.25-0.91) (Figure 3).

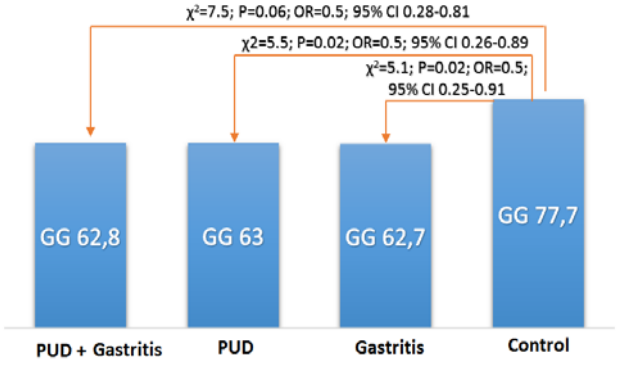

Figure 3. Frequency of occurrence (%) of G/G genotype rs1800471 of TGFb1 gene in patients with gastroduodenal diseases and conditionally healthy persons of Uzbek nationality

Against the background of a significant decrease in the carriage of the prototype homozygous genotype G/G in patients with gastroduodenal diseases, the proportion of carriers of the heterozygous G/C genotype increased by approximately 1.6 times, from 21.6 to 34.4% ($\chi2 = 9.2$, P = 0.002, OR = 2.4, 95% CI 1.35-4.0) both due to patients with DU ($\chi2 = 5.9$, P = 0.01, OR = 2.2, 95% CI 1.15-4.33), and due to patients with ChG ($\chi2 = 7.9$, P = 0.005, OR = 2.6, 95% CI1.31-5.15) (Figure 4), which obviously indicates a reliable association between the heterozygous G/A genotype of polymorphism of rs1800471 TGFb1 gene with development of the DUHB and chronic ha tritium. The pathogenetic realization of this mutation is probably the decrease in the content of the anti-inflammatory cytokine TGF-β1 in the structural elements of the gastric mucosa and PDC. According to a study by Ohgushi M. et al. (2005), any defects in the metabolic chain of the TGF-β-regulated apoptosis-stimulating biomechanism of epithelial cell death can act as a factor contributing to the development of a stomach disease.

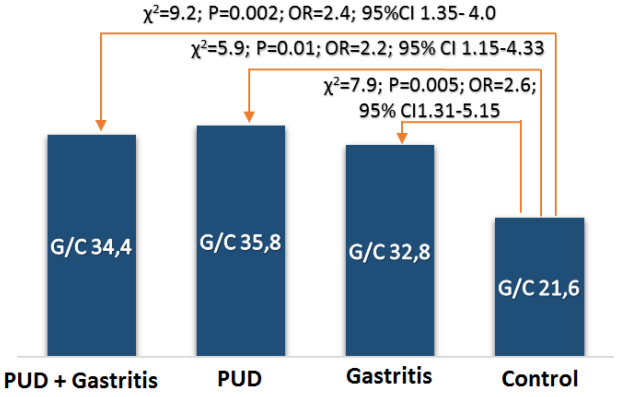

Figure 4. The frequency of occurrence (%) of the genotype rs1800471 of the gene TGFb1 in patients with gastroduodenal diseases and conditionally healthy persons of Uzbek nationality

Since the production of the cytokine TGF-β1 is most depressed in the presence of the homozygous genotype C/S at the locus of +915 [15], and the hereditary defect caused by this mutation is negatively manifested, primarily in the regeneration of the epithelial cover of the gastric mucosa [14], we noted this rare genotype mainly in patients with ChG (3 cases out of 4). It is experimentally established that in rats the administration of the cytokine TGF-β1 has a moderate gastroprotective effect and plays a significant role in the healing of gastric ulcers [13].

The frequency of genotypes of the polymorphic region rs1800471 of the TGFb1 gene in the Uzbek population revealed by us differs significantly from the analogous data typical for different populations of Europoid and Asians (Table 2).

Table 2. The genotype frequency of the polymorphic region rs1800471 of the TGFB1 gene in relatively healthy donors in different populations

Group	G/G		G/C		C/C	
	n	%	n	%	n	%
Uzbekistan, n=139	108	77.7	30	21.6	1	0.7
Germany, n=1211	1063	87.8	141	11.6	7	0.6
χ^2-тест	df=2; $t_{стат}$=11.228; $t_{крит}$=9.21; p=0.004, p<0.01					
Northern Ireland and France (ECTIM investigation), n=629	546	86.8	81	12.9	2	0.3
χ^2-test	df=2; $t_{стат}$=7.547; $t_{крит}$=5.991; p=0.023, p<0.05					
Taiwan, n=124	115	92.7	8	6.5	1	0.8
χ^2-test	df=2; $t_{стат}$=12.141; $t_{крит}$=9.21; p=0.003, p<0.01					
Iran, n=78	71	91.0	7	9.0	0	0
χ^2-test	df=2; $t_{стат}$=6.295; $t_{крит}$=5.991; p=0.043, p<0.05					

Thus, in relatively healthy individuals of Uzbek nationality, carriers of genotypes G/C and C/C were almost 2-3 times more frequent. This new information, obtained for the first time from the population of Central Asia, certainly

complements the database reflecting the differences in the nature of the cohesion of polymorphisms of the TGFB1 gene in different populations.

In addition, the phenomenon of the almost doubling of the carriers of genotypes associated with the inhibition of the expression of the cytokine TGF-β1 in the Uzbek population, as compared to European populations, is an additional argument that indirectly confirms the assumption that the polymorphism of the TGFB1 gene may be a susceptibility factor organism to Helicobacter pylori infection [15]. The fact is that, according to the results of an observational study conducted in 2005, the prevalence of infection caused by Helicobacter pylori in Uzbekistan is about 80% [16], while this figure in European countries is 34.7% (95% CI: 30, 2-39.3) [17]. There is a report that the polymorphism of the gene TGF-β1 T869C is associated with susceptibility to diseases caused by Helicobacter pylori [18]. Another clinical study showed an increased risk of developing precancerous diseases of the stomach in individuals with CagA-positive Helicobacter pylori strains and polymorphism of the TGF-β1 C-509T promoter [19]. Moreover, immunohistochemistry methods found suppression of TGF-β1 expression in epithelial cells of the stomach against the background of Helicobacter pylori infection. Compared with healthy people and patients with ChG not associated with Helicobacter pylori, a significant decrease in the concentration of TGF-β1 in gastric tissue is observed in persons with Helicobacter-associated gastritis [20]. In addition, a low content of TGF-β1 in the glands of the gastric mucosa is determined with Helicobacter pylori associated DU, and after eradication of the infection, its significant increase is noted. In contrast, in patients without helicobacter infection in gastropathy caused by non-steroidal anti-inflammatory agents, the growth of immunoreactive TGF-β1 in the surface and deep glands of the gastric mucosa was observed [13].

Table 3. Correspondence of the distribution of the genotypes of rs1800471 polymorphism of the TGFB1 gene to the Hardy-Weinberg equation in the study groups

Genotypes	Frequency of occurrence of genotypes		χ^2-test	p
	the observed	expected		
Patients with DU and ChG, n=148				
G/G	0.63	0.64	0.30	0,3
G/C	0.34	0.32	0.3	
C/C	0.03	0.04	0.6	
Total	1.0	1.00	0.93	
Healthy donors, n=139				
G/G	0.78	0.78	0.90	0,5
G/C	0.22	0.20	0.10	
C/C	0.07	0.01	0.38	
Total	1.00	1.00	0.49	

The frequency (Hobs) of the distribution of the genotypes of the polymorphism rs1800471 of the TGFB1 gene in the combined group of patients and in the control group of donors corresponded to the expected distribution (Hexp) according to the Hardy-Weinberg equation (P> 0.05) (Table 3).

The heterozygosity index for the observed (Hobs) and the expected (Hexp) indices in patients with gastroduodenal diseases was higher in this polymorphism than in healthy donors (0.34 and 0.32 vs. 0.22 and 0.20, respectively). Moreover, there is a tendency to a slight excess of heterozygosity in both compared groups (the indicator of the relative deviation of heterozygosity D was correspondingly +0.06 and +0.1) (Table 4).

Thus, our results suggested that the functionally unfavorable C allele and heterozygous G/C genotype of polymorphism rs1800471 of TGFB1 gene are significant markers of increased risk of formation of DU and ChG in Uzbekistan.

Table 4. The difference between the expected and observed heterozygosity frequencies

Groups	Heterozygosity		D*
	the observed	Expected	
Basic	0.34	0.32	+0.06
Control	0.22	0.20	+0.1

Note: D=(0.34-0.32)/0.32 = for the main group;
D=(0.22-0.20)/0.20 = for the control group

The carriage of the functionally unfavorable homozygous genotype C/S according to the calculated odds ratio, by 1.7 and 6.5 times statistically improperly increases the risk of development of DU and ChG, respectively.

These data indicate a strong tendency towards association of a rare genotype with the development of these diseases, especially ChG, where OR = 6.5, which may be explained by the inadequate number of patients with this genotype.

The favorable homozygous genotype G/G of this polymorphism has a protective effect on the risk of these diseases.

3. Conclusions

The carrier of the heterozygous G/C genotype of the TGFb1 gene (rs1800471) is associated with a high risk of development of DU and ChG. The homozygous genotype G/G possesses a protective anti-inflammatory role in the pathogenesis of ulcerative and inflammatory lesions of the gastric mucosa and duodenum. Relatively healthy people of Uzbek nationality are 2-3 times more likely to have carriers of genotypes G/C and C/C in comparison with different populations of Europoid and Asians. This new information, obtained for the first time from the population of Central Asia, complements the database reflecting the differences in the nature of the adhesion of polymorphisms of the TGFB1 gene in different populations.

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