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ROLE OF SINGLE NUCLEOTIDE GENE POLYMORPHISMS IN THE DEVELOPMENT OF ULCERATIVE COLITIS

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The purpose of the work was to study the features of the IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C> A), IL10 (C-819T), IL10 (G- 1082A), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) genes polymorphic variants influence on the development of ulcerative colitis in patients. The total of 53 patients with ulcerative colitis were examined, the control group included a random sample of 49 healthy persons. Association of the ulcerative colitis development with the incidence of single nucleotide polymorphism of IL10 wild genotype gene (rs1800896), homozygous G/G genotype of single nucleotide polymorphism of the Tlr4 gene (rs4986790), the frequency of the T allele in the IL1 gene (rs1143627), C allele in the IL1 gene (rs 16944) and IL10 (rs1800872), which contributed to the disturbance and imbalance in the production of pleiotropic cytokines IL1 and IL10, predisposing to the development of ulcerative colitis and aggravating the course of the disease. The work shows associative links for single nucleotide polymorphism of Tlr4 gene (rs4986791) with the development of nonspecific ulcerative colitis both according to the multiplicative model with the C allele and according to the general inheritance model with the wild type of C/C genotype, which confirms the importance of this single nucleotide polymorphism in the development of the disease.

Key words: nonspecific ulcerative colitis, single nucleotide gene polymorphism, allele, genotype.

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Despite the advances in modern medicine, inflammatory bowel diseases (IBD) remain an unsolved problem. The prevalence as well as the incidence of IBD in different regions of the world has a wide range enough. The incidence of nonspecific ulcerative colitis (NUC) is detected in 1.25 - 20.3 new cases per 100 thousand of inhabitants, the prevalence is 21-268 cases per 100 thousand of inhabitants [2]. Crohn's disease (CD) is much less common and is detected in 2-4 cases per 100 thousand of inhabitants, the prevalence is 10-150 per 100 thousand of population [3].

Today IBD belong to the group of multifactorial diseases, often with a comorbid course, which development is effected by combined and modifying impact of genetic and environmental factors [1]. Today, there is evidence of the influence of 163 gene polymorphisms on the IBD development [8], which are primarily responsible for the integrity of the intestinal mucosa epithelium and the body's timely immune response to the influence of the external environment. In favor of a genetic predisposition to the IBD development, there are registered family cases, which range from 6 to 30%, and the same type of changes in 122 identical genes, identified in the study of epithelial cells of the intestinal mucosa, according to the data of the Kiel University (Germany) [4].

Speaking about the importance of genetic predisposition in the development of IBD [11], most frequently we talk about single nucleotide gene polymorphisms (SNPs), which can affect the rate of gene transcription, change the binding of transcription factors, mRNA level and its stability [9], affecting the immune response. Signal pattern-recognition receptors, as well as possible single nucleotide polymorphisms of genes responsible for the work of these structures, have a direct impact on the development of IBD. Thus, the researchers confirmed the influence of the SNP NOD2 / CARD15 gene (2104 C / T, 2722 G / C, G908R, Leu3020fsinsC) on the development of Crohn disease (CD), which is responsible for the recognition of intracellular pathogens that regulate inflammatory reactions in activation of nuclear factor NF-kB [6].

Many authors have identified the correlation between the development of both NUC and CD and SNPs of toll-like receptors genes (TLr) [6, 7], which play a major role in the genetic predisposition to changes in bacterial colonization. Thus, the correlation of IBD with SNP of TLr 2 and TLr 4 genes was revealed. SNP of the TLr 4 gene Asp299Gly changes the resistance of the microorganism to gram-negative bacteria, thereby contributing to the onset of dysbiosis, which is often associated with IBD. The occurrence of SNP in the TLr 2 gene alters the susceptibility of the intestinal mucosa epithelium to infectious agents. The emergence of SNP Arg753Gln in the TLr 2 gene raises the propensity to develop a complicated course of infections.

In the development of IBD, the role of SNP genes has been proven in secreting cytokines [5, 10, 12], which provide local interactions of the immune system cells with specific cellular receptors. In the

presence of genetic changes responsible for the secretion of cytokines such as TNF - α, IFN - γ, transforming growth factor (TGF - β), IL 1β, IL 5, IL 6, IL 8, IL 10, IL 13, IL 17, IL 22, the structure of the epithelial barrier may change. In future, such disorders can contribute to the penetration of pathogenic microorganisms into epithelial cells and cause the onset of inflammatory or proliferative changes in the intestine.

The purpose of the work was to study the features of some single nucleotide gene polymorphisms correlation with the development of nonspecific ulcerative colitis.

Materials and methods. In order to assess the possible effect of SNP on predisposition to the development of NUC, the detection frequency of genotypes and alleles of SNP genes IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C> A), IL10 (C-819T), IL10 (G-1082A) Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) was studied in 53 patients with NUC treated at the Poltava N.V. Sklifosovsky Regional Clinical Hospital. The control group included a random sample of 49 healthy individuals. The mean age of patients was (35.4±3.9) years, the control group's mean age was (31.8±4.1) years. Among patients with IBD, men accounted for 28 (52.8%) patients, women - 25 (47.2%) patients, the onset of the disease was most frequently detected at the age of 18-43 years - 39 (73.6%) patients, the duration of the disease more frequently ranged from 5 to 10 years - 24 (45.3%) patients. The diagnosis was confirmed clinically, instrumentally, morphologically. The examination revealed a reliaby more frequent lesion in the colon's left part - 31 (58.5%) patients, a mild degree of process activity was found in 25 (47.2%), moderate in 22 (41.5%) patients, severe disease activity - 6 (11.3%) patients.

To isolate SNPs in the human genome, the polymerase chain reaction (PCR) technique was used. By means of phenol-chloroform extraction method DNA was isolated, which was subsequently washed with 70% ethanol solution. After drying in air, further dissolution was carried out in deionized water, storage took place at a temperature of -20° C with a Rearch PCR Thermal Cycler (Corbett, Australia), using "Litech" genotyping kits (Russia) according to the instructions, amplification of the sequences was carried out using PCR.

To analyze the obtained amplification data, electrophoresis in 2% agarose gel was used, which was stained with ethidium bromide; a UV transilluminator was used for scanning. Genotyping was performed in the Laboratory of Pathophysiology and Immunology of the D.F. Chebotarev Institute of Gerontology, NAMS of Ukraine.

To find the correlation between the NUC development and SNP of genes when analyzing the allele frequency, a multiplicative model was used in cases of observance of the Hardy-Weinberg equilibrium and a general inheritance model - when analyzing the frequency of genotypes when the equilibrium was not observed. Statistical analysis was performed using the EXCEL package of standard software for statistical analysis; to assess the reliability of differences in the groups, the Student's t criteria were used.

Results of the study and their discussion. Так как НЯК относится к полигенным заболеваниям, проанализировали частоту выявления SNP генов, ответственных за секрецию цитокинов и работу толлподобных рецепторов, которые могут способствовать активации воспаления, как наиболее важных в патогенезе НЯК. Для полноценного анализа возможного взаимодействия развития НЯК с вариантами SNP генов IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C>A), IL10 (C-819T), IL10 (G-1082A), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly), проведен подсчет соответствия полученных данных равновесию Харди-Вайнберга (тест χ^2 при уровне значимости df=1).

Since NUC belongs to polygenic diseases, we analyzed the frequency of detecting SNP genes responsible for the secretion of cytokines and the work of toll-like receptors, which can promote the activation of inflammation, as the most important in the pathogenesis of NUC. For a complete analysis of the possible interaction of NUC development with SNP variants of the IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C> A), IL10 (C-819T), IL10 (G -1082A), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly), the correspondence of the obtained data to the Hardy-Weinberg equilibrium was calculated (test χ^2 at a significance level of df = 1).

Among the examined patients with nonspecific ulcerative colitis, the Hardy-Weinberg condition was fulfilled both for the observed cases and for the control patients, except for substitutions ($p < 0.05$). When assessing the compliance with this equilibrium in the frequency distribution of the alleles associations, for some SNP genes, no confirmation was found in the study and the control groups. The obtained results of the control group are presented in table 1.

Table 1

Nonobservance of the Hardy-Weinberg equilibrium in the control group of healthy individuals

No	gen	genotype	control	HWE	χ2	p
1.	IL10 C-819T	Genotype *C/C*	0.449	0.525	7.09	0.008
		Genotype *C/T*	0.551	0.399		
		Genotype *T/T*	0.000	0.076		
2.	IL10 G-1082A	Genotype *A/A*	0.061	0.250	27.94	1.0E-7
		Genotype *A/G*	0.878	0.500		
		Genotype *G|G*	0.061	0.250		
3.	Tlr4 Asp299Gly	Genotype *A/A*	0.245	0.387	18.03	2.0E-5
		Genotype *A/G*	0.755	0.470		
		Genotype *G|G*	0.000	0.143		

As it is seen from the presented table, in the control group of healthy individuals, a shift in the genotypes frequency from the normal distribution was revealed: rs 1800871 (IL 10, $\chi^2 = 7.09$, $p < 0.008$); rs 100896 (IL 10, $\chi^2 = 27.94$, 1.0E-7); rs 4986790 (Tlr4, $\chi^2 = 18.03$, 2.0E-5), which indicates that there is no correspondence to the Hardy-Weinberg equilibrium for the SNPs of the IL10 (C-819T), IL10 (G-1082A), Tlr4 (Asp299Gly) genes.

Inconsistency with the Hardy-Weinberg equilibrium is also evident in the group of patients with NUC. According to the obtained results of the study, there was a shift in the frequency of genotypes from the normal distribution in the group of patients with IBD for SNP of IL10 (G-1082A) and Tlr4 (Asp299Gly) genes. Thus, in the group of patients with IBD, when analyzing the SNP data of the rs 1800896 (IL 10) gene,it was found that $\chi^2 = 5.18$, $p < 0.02$, and for SNP of the rs 4986790 (Tlr4) gene - $\chi^2 = 8.03$, $p < 0.005$, which confirms the impossibility of using the multiplicative model to identify the correlation between the development of NUC and SNP data, since the Hardy-Weinberg equilibrium is not observed. The correlation between the above genes SNP and NUC was analyzed using a general inheritance model taking into account the frequency of genotypes.

According to our data, the association of allele frequencies of genes with NUC was revealed by SNPs of genes IL1 (T-31C), IL1 (T-511C), IL10 (592C> A), Tlr4 (Thr399ile). The results are presented in table 2.

Table 2

Multiplicative inheritance model for a sample of patients with NUC

gen	allele	NUC	control	χ2	*p*	value	OR95%CI
IL1rs1143627	C	0.538	0.673	3.92	0.05	0.56	0.32 – 1.00
	T	0.462	0.327			1.77	1.00 – 3.13
IL1 rs 16944	C	0.491	0.357	3.71	0.05	1.73	0.99 – 3.04
	T	0.509	0.643			0.58	0.33 – 1.01
IL10rs1800872	A	0.689	0.816	4.43	0.04	0.50	0.26 – 0.96
	C	0.311	0.184			2.01	1.04 – 3.87
Tlr 4rs4986791	C	0.934	0.796	8.45	0.004	3.63	1.46 – 9.01
	T	0.066	0.204			0.28	0.11 – 0.69

In accordance with the presented table, in patients with NUC, the correlation with the frequency of SNP alleles of genes responsible for the stability of the intestinal mucosa epithelium and regulation of cytokine production was revealed. The association of the disease was revealed by the multiplicative model of inheritance for substitutions of the T allele rs1143627 (IL1, $\chi2 = 3.92$, $p < 0.05$), the C allele rs 16944 (IL1, $\chi2 = 3.71$, $p < 0.05$), and the C allele rs1800872 (IL10, $\chi2 = 4.43$, $p < 0.04$), allele C rs4986791 (Tlr 4, $\chi2 = 8.45$, $p < 0.004$), compared to healthy persons.

The said genetic changes confirm the influence of the cytokine imbalance on the development and course of NUC, predict the possibility of a more severe and complicated course of the disease. The revealed correlation in patients with NUC with the SNP of the Tlr 4 gene (rs 4986791), C allele, confirms the influence of dysbiotic disorders on the development of the disease, possibly causing an inadequate response to the ongoing therapy.

When analyzing the general model of SNP substitutions inheritance in genes of patients with NUC, an associative relationship was revealed with 3 substitutions. The result is shown in table 3.

Table 3

General inheritance model in patients with NUC

gen,SNP	genotype	genotype frequency		$\chi 2$	p	OR	
		NUC	control			value	95%CI
Control group –healthy persons (n=49)							
IL10 rs1800896	A/A	0.302	0.061	10.21	0.006	6.63	1.79 –24.50
	A/G	0.623	0.878			0.23	0.08 – 0.64
	G/G	0.075	0.061			1.25	0.27 – 5.90
Tlr 4 rs4986791	C/C	0.868	0.633	8.30	0.02	3.82	1.43 –10.21
	C/T	0.132	0.327			0.31	0.12 – 0.85
	T/T	0.000	0.041			0.18	0.01 – 3.79
Tlr4 rs4986790	A/A	0.679	0.245	31.98	1.0E-7	6.53	2.74 –15.58
	A/G	0.208	0.755			0.08	0.03 – 0.22
	G/G	0.113	0.000			13.55	0.74 -247.18

According to the presented table, the highest associative risk of developing NUC was determined with carrying SNP in the Tlr4 gene (rs4986790). When compared to the control group, SNPs of the homozygous genotype G / G of the Tlr4 gene (rs4986790) prevailed in patients with NUC ($\chi 2 = 31.98$, $p < 0.05$, OR = 13.55, 95% CI: 0.74 - 247.18), which may indicate the correlation of this polymorphism with the risk of developing NUC, confirms the influence of microbiota stability on the course and development of pathological changes in the intestine, a possible tendency to dysbiotic disorders of the intestine.

In addition, in patients with NUC, the dominance of the wild homozygous genotype A / A in the IL10 gene (rs1800896) was revealed ($\chi 2 = 10.21$, $p < 0.006$, OR = 6.63.95% CI: 1.79 - 24.50). Also, the obtained results of the analysis revealed an association of the risk of developing NUC with the SNP substitution carriership in the Tlr4 gene (rs4986791), wild type C / C genotype ($\chi 2 = 8.30$, $p < 0.02$, OR = 3.82, 95% CI: 1.43–10.21), and the data were consistent with the results of the multiplicative model of inheritance, which may confirm the special role of the above SNP in the pathogenesis of NUC development.

When using the multiplicative and general models of inheritance to analyze the possible predisposition to the development of NUC for the SNP variants of the IL6 (C-174 G) and Tlr2 (Thr399ile) genes, no association with the disease was found, compared to the control group of healthy individuals, which does not contradict the data of other authors [6, 7] and requires further diagnostic search. Identification of allelic polymorphisms of the genes responsible for the production of cytokines in patients with NUC can facilitate prescription of timely personalized adequate therapy, which will prevent further disease progression and the occurrence of complications in our patients. SNPs of genes in IBD can influence the development of an individual immune response and alter the production of cytokines responsible for the inflammatory process. In our patients, the correlation of the disease was revealed both with the frequency of the IL10 SNP of the wild genotype (rs1800896) and with the allelic polymorphism of T allele in the IL1 gene (rs1143627), C allele of the IL1 (rs 16944) and IL10 (rs1800872) genes, which confirms the data of foreign researchers [9 ,12]. These changes can affect the work of the pleiotropic cytokines IL1 and IL10, play an important role in the process of inflammation and formation of the body's defensive reactions. In addition, the multifactorial effect of the genetic SNP in our patients was confirmed by the identification of the disease association with SNP of the Tlr4 gene (rs4986790), which regulates the mechanisms of pathogenic microorganisms recognition and, when they change, can also alter the immune response, contributing to an increase in the production of proinflammatory cytokines and chemoxins. In contrast to foreign authors [7], in which associations of NUC with SNP of the Tlr4 gene (rs4986791) were only detected in allelic models, according to our data, the correlation was determined both by multiplicative and general inheritance models.

Most researchers of NUC, note the difficulties in diagnosing the disease. Timely identification of gene polymorphisms responsible for the stability of the intestinal mucosa epithelium, such as SNP of the Tlr4 gene, secretion of pro-inflammatory and anti-inflammatory cytokines (IL1, IL10), will permit earlier suspecting the patient's tendency to IBD, the possibility of this disease onset, and timely prescribing appropriate adequate therapy.

Conclusion

Thus, the results obtained confirm the relationship between the development of NUC and SNP of genes responsible for the production of cytokines and the epithelium stability of the colon mucosa. In the examined patients, an association was found between the development of NUC with the frequency of wild genotype SNPs in the IL10 gene (rs1800896), homozygous G / G genotype SNPs of the Tlr4 gene (rs4986790), the frequency of the T allele in the IL1 gene (rs1143627), C allele in the IL1 (rs 169) and

IL10 (rs1800872) genes, which contributed to the disturbance and imbalance in the production of cytokines, predisposing to the development of NUC and aggravating the disease course. Associations for the SNP of the Tlr4 gene (rs4986791) with the development of NUC were revealed both by the multiplicative model with the C allele and by the general inheritance model with the wild type C / C genotype, which confirms the importance of this SNP in the development of the disease.

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Реферати

РОЛЬ ОДНОНУКЛЕОТИДНИХ ПОЛІМОРФІЗМІВ ГЕНІВ У РОЗВИТКУ НЕСПЕЦИФІЧНОГО ВИРАЗКОВОГО КОЛІТУ

Кир'ян О.А., Дорофєєв А.Е., Хайменова Г.С., Дорофєєва А.А.

Метою дослідження було вивчення особливості впливу поліморфних варіантів генів IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C> A), IL10 (C-819T), IL10 (G-1082A) Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) на розвиток неспецифічного виразкового коліту у хворих. В обстеження було залучено 53 пацієнта, контрольну групу склала випадкова вибірка з 49 здорових осіб. У наших пацієнтів виявлено асоціацію розвитку неспецифічного виразкового коліту з частотою поліморфного варіанту гена IL10 дикого генотипу (rs1800896), гомозиготного генотипу G/G поліморфного варіанту гена Tlr4 (rs4986790), частотою алелі Т в гені IL1 (rs1143627), алелі С в генах IL1 (rs 16944) і IL10 (rs1800872), які сприяли порушенню і дисбалансу у виробленні плейотропних цитокінів IL1 и IL10, модифікуючи перебіг неспецифічного виразкового коліту, впливаючи на його розвиток. В роботі показані асоціативні зв'язки для однонуклеотидного поліморфізму гена Tlr4 (rs4986791) з розвитком неспецифічного виразкового коліту як по мультипликативній моделі з алеллю С, так і за загальною моделлю успадкування з диким типом генотипу С/С, що підтверджує важливість даного однонуклеотидного поліморфізму в розвитку захворювання.

Ключові слова: неспецифічний виразковий коліт, однонуклеотидний поліморфізм генів, аллель, генотип.

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РОЛЬ ОДНОНУКЛЕОТИДНЫХ ПОЛИМОРФИЗМОВ ГЕНОВ В РАЗВИТИИ НЕСПЕЦИФИЧЕСКОГО ЯЗВЕННОГО КОЛИТА

Кирьян Е.А., Дорофеев А.Е., Хайменова Г.С., Дорофеева А.А.

Целью нашего исследования было изучить особенности влияния полиморфных вариантов генов IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C>A), IL10 (C-819T), IL10 (G-1082A), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) на развитие неспецифического язвенного колита у больных. Были обследованы 53 пациента с неспецифическим язвенным колитом, контрольную группу составила случайная выборка из 49 здоровых людей. Выявлена ассоциация развития неспецифического язвенного колита с частотой однонуклеотидного полиморфизма гена IL10 дикого генотипа (rs1800896), гомозиготным генотипом G/G однонуклеотидного полиморфизма гена Tlr4 (rs4986790), частотой аллеля Т в гене IL1 (rs1143627), аллеля С в генах IL1 (rs 16944) и IL10 (rs1800872), которые способствовали нарушению и дисбалансу в выработке плейотропных цитокинов IL1 и IL10, предрасполагая к развитию неспецифического язвенного колита и усугубляя течение болезни. В работе показаны ассоциативные связи для однонуклеотидного полиморфизма гена Tlr4 (rs4986791) с развитием неспецифического язвенного колита как по мультипликативная модели с аллелью С, так и по общей модели наследования с диким типом генотипа С/С, что подтверждает важность данного однонуклеотидного полиморфизма в развитие заболевания.

Ключевые слова: неспецифический язвенный колит, однонуклеотидный полиморфизм генов, аллель, генотип.

Рецензент Костенко В.О.