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CONTENTS

ЗМІСТ

CLINICAL MEDICINE

КЛІНІЧНА МЕДИЦИНА

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SEARCH FOR DIAGNOSTIC RELATIONSHIPS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME AND COLORECTAL POLYPS

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The article describes the problems of diagnosis of irritable bowel syndrome and adenomatous colorectal polyps. The purpose of the study was to identify possible hereditary factors in the development of irritable bowel syndrome and adenomatous colorectal polyps in adults. It was found that single nucleotide polymorphisms of IL-10 wild genotype gene (rs1800871), homozygous genotype of IL-10 gene (rs1800896), heterozygous genotype of IL-1 gene (rs 16944), wild and homozygous genotypes of CHEK2 gene (rs 17879961) are associated with the development of irritable bowel syndrome. Single nucleotide polymorphisms of IL-10 wild genotype gene (rs1800896) and MMP 9 heterozygous genotype gene (rs11697325) had a significant effect for adenomatous colorectal polyps. The overall effect and relationship for patients with both diseases was determined by Tlr2 (rs 5743708), Tlr4 (rs4986790) and TgFb1 (rs 1800471) gene polymorphisms. The study results show that gene polymorphisms can affect both each disease individually, and be a unifying factor influencing the development of irritable bowel syndrome and adenomatous colorectal polyps, and also affect the general mechanisms of progression and possible neoplastic transformation on the background of functional disease.

Key words: irritable bowel syndrome, adenomatous colorectal polyps, single nucleotide polymorphism, gene.

О.А. Кир`ян

ПОШУК ДІАГНОСТИЧНОГО ВЗАЄМОЗВ'ЯЗКУ У ХВОРИХ ІЗ СИНДРОМОМ ПОДРАЗНЕНОГО КИШЕЧНИКА ТА ПОЛІПАМИ ТОВСТОЇ КИШКИ

У статті описані проблеми діагностики синдрому подразненої кишки та аденоматозних поліпів товстої кишки. Метою дослідження було виявлення можливих спадкових факторів розвитку синдрому подразненої кишки та аденоматозних поліпів товстої кишки у дорослих. Було встановлено, що з розвитком синдрому подразненої кишки мають асоціацію однонуклеотидні поліморфізми дикого варіанту гену IL-10 (rs1800871), гомозиготного варіанту гену IL-10 (rs1800896), гетерозиготного варіанту гену IL-1 (rs 16944), дикого та гомозиготного варіантів гену CHEK2 (rs 17879961). Для аденоматозних поліпів товстої кишки значний ефект мали однонуклеотидні поліморфізми дикого типу гену IL-10 (rs1800896) і гетерозиготного варіанту гену MMP 9 (rs11697325). Загальний вплив та взаємозв'язок для пацієнтів із обома захворюваннями визначали поліморфізми генів Tlr2 (rs 5743708), Tlr4 (rs4986790), TgFb1 (rs 1800471). Результати досліджень свідчать, що поліморфізми генів можуть впливати як на кожне захворювання окремо, так і бути об'єднуючими факторами впливу на розвиток синдрому подразненої кишки та аденоматозних поліпів кишечника, а також впливати на загальні механізми появи прогресування і можливої неопластичної трансформації на тлі функціонального захворювання.

Ключові слова: синдром подразненої кишки, аденоматозні поліпи товстої кишки, однонуклеотидний поліморфізм, ген.

The work is a fragment of the research project "Features of the course, prognosis and treatment of comorbid conditions in diseases of the internal organs, with account of genetic, age and gender aspects", state registration No. 0118U004461.

The prevalence and incidence of intestinal diseases is determined in Ukraine [3]. The number of cases of not only functional diseases, such as irritable bowel syndrome (IBS), [1, 13], but also organic pathology of the intestine, such as adenomatous colorectal polyps (ACPs), which have a high risk of neoplastic transformation [5], is increasing. Irritable bowel syndrome (The Rome IV criteria, 2016) [12] is a common chronic functional bowel disease, which affects about 20 % of the adult population [13]. The formation of ACPs, which are found in about 40 % of the western population is a consistent process. When the disease progresses, with the aberrant proliferation in epithelial cells of the colonic mucosa (CM) [4], it can lead to the occurrence of malignant neoplasms. Therefore, timely detection of ACPs is considered a secondary prevention of bowel cancer. Given the often asymptomatic course of ACPs, it is very important to suspect the contraction of adenoma in patients with IBS, as microinflammatory processes and dysbiotic changes, detected in IBS [13], can provoke the appearance and progression of adenomatous polyps.

There are many theories about the cause of IBS and ACPs multifactorial diseases that sometimes have significant similarities in the pathogenetic levers of influence, which appearance is influenced by both external factors and dysbiotic disorders and hereditary mechanisms [3, 9, 13]. Genetic predisposition can create a negative background for other factors and be one of the main triggers for the disease development. Among the markers of genetic predisposition to the contraction of both IBS and ACPs, most scientists focus on single nucleotide polymorphisms (SNPs), which can affect the appearance of diseases and cause the organic changes on the background of functional diseases [8]. Among SNPs, which could potentially have a major impact on both IBS and ACPs, researchers have identified polymorphisms that regulate the

functioning of cytokines such as IL-1β [2, 8], IL-10 [8, 15], TgFb1 [11]. The influence of SNP of genes, which are responsible for the Toll-like receptors (TLRs TLr2, Tlr4) functioning, on IBS and ACPs development is also possible, taking into account their properties in the induction of the innate immune response to microbial ligands [14]. Both IBS and ACPs are often accompanied by dysbiotic disorders, and SNP data can modify the CM response to bacterial and viral pathogens and trigger an inflammatory response cascade. The work of researchers is known to confirm the connection between the SNP of the MMP9 gene and the regulation of the inflammatory process in the intestinal epithelium. This SNP can have an impact on the ACPs development and low-grade inflammation in IBS by modifying the processes of CM epithelial healing, proliferation, differentiation and apoptosis [10]. In addition, SNP of the CHEK2 gene, which is involved in cell cycle regulation and DNA repair, affects cell and tissue repair, may play an important role in the development of both IBS and ACPs, to determine the susceptibility to bowel cancer [6] against the background of these diseases. Therefore, timely detection of genetic predisposition to the contraction of both IBS and ACPs, in-depth search and identification of relationships between diseases can help to prevent further neoplastic transformation and disease progression.

The purpose of the work was to study possible general hereditary triggers of the development of irritable bowel syndrome and adenomatous colorectal polyps in patients of the Poltava region.

Materials and methods. To achieve this purpose, we examined 82 patients in the M.V. Sklifosovsky Poltava Regional Clinical Hospital. Their mean age was 43.4±6.7 years, the ratio of men and women – 1: 1.4. All patients were divided into 2 groups, group 1 included patients with IBS – 46 (56.1 %), group 2 included patients with ACPs – 36 (43.9 %). The control group consisted of 49 healthy individuals. The mean age in patients with IBS was 37.6±6.8 years, in patients with ACPs – 48.7±5.4 years, in the control group – 33.4±6.1 years without a significant difference between groups ($p>0.05$). There was no significant gender difference in the groups. The mean disease duration was 7.63±4.11 years (from 6 months to 12 years). In patients with IBS, the diagnosis was established in accordance with the Rome criteria IV, 2016 [12]. The diagnosis in patients with ACPs was confirmed endoscopically, taking into account morphological and histological conclusions.

In order to identify the genetic predisposition relationship between patients with IBS and ACPs, patients underwent blood tests for SNP of 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), TgFb1 (Arg25Pro), Tp53 (pro72Arg), Tp53 (pro47ser), MMP 9 (A-8202G), CHEK2 (ile157Thr) and Timp 1 (C536T) to determine the wild, heterozygous and homozygous types of SNP of genes and to analyze their possible influence on the development of the disease. The polymerase chain reaction (PCR) method was used to isolate SNPs, according to which DNA was isolated by phenol–chloroform extraction method, and then washed with 70 % ethyl alcohol solution. DNA was stored at 20°, before which it was dissolved in deionized water and dried in air. Sequence based amplification was performed with a Rearch PCR Thermal Cycler (Corbett, Australia). “Litech” genotyping kits (Russia) were used according to the instructions. 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.

In order to determine the significant difference in the examined patients of different groups, statistical analysis was performed using the EXCEL package of standard software for statistical analysis; the Student's t criteria and Student's tables (reliability value $p<0.05$) were used.

Results of the study and their discussion. Taking into account the possible influence of SNP of genes responsible for cytokine stability on the development of IBS and ACPs, the detection rate of SNP genes IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), IL10 (592C>A), IL10 (C-819T), IL10 (G-1082A) was analyzed in patients (table 1).

According to the obtained data, the SNP analysis of genes IL1 (T-31C), IL1 (T-511C), IL6 (C-174 G), which are responsible for the functioning of proinflammatory cytokines, all types of SNPs were identified in the studied groups. Heterozygous SNP of IL1 (rs 16944) gene was more often found in patients with IBS – 28 (60.9 %) patients ($p<0.05$), compared with a group of healthy individuals, which may have had an impact on the predisposition to IBS. Among the studied SNPs of genes responsible for the functioning of anti-inflammatory cytokines, the wild-type SNP of gene IL-10 (rs1800872) was detected with the same frequency, the SNP of IL-10 gene (rs1800896) was found significantly more often in patients with ACPs – 17 (47.2 %) cases ($p<0.01$), compared with the control group and patients with IBS. Wild-type SNP of gene IL-10 (rs1800871) was more often found in patients with IBS – 30 (65.2 %) patients, compared with the group of healthy individuals ($p<0.05$). Heterozygous SNP of the IL-10 (rs1800871)

gene was less often detected – 13 (28.3 %) patients with IBS, compared with the ACPs group and healthy individuals ($p<0.05$), which may have confirmed the significance of this SNP as a factor influencing the IBS development. The heterozygous SNP of the IL-10 (rs1800896) gene was significantly lower in both groups ($p<0.05$) compared to the control group, which may have been the link between these diseases. Homozygous SNP of gene IL-10 (rs1800896) was not detected in ACPs. There was also no homozygous SNP of the IL-10 (rs1800871) gene in the control group of healthy individuals, which confirms the importance of this SNP in the development of intestinal diseases. In addition, the more frequent detection of homozygous SNP of IL-10 (rs1800896) in patients with IBS ($p<0.05$), confirms the relationship of this polymorphism with the onset of the disease.

Table 1

Features of SNP in genes responsible for pro- and anti-inflammatory cytokines in patients with different subtypes of IBS and ACPs

SNP of genes		IBS (n=46)		ACPs (n=36)		Control (n=49)	
gene	type	n	%	n	%	n	%
IL-1 (T-31C) ***rs 1143627***	CC	16	34.8	16	44.4	21	42.9
	CT	25	54.3	11	30.6*	24	48.9
	TT	5	10.9	9	25.0	4	8.2
IL-1 (T-511C) ***rs 16944***	CC	2	4.3	4	11.1	7	14.2
	CT	28	60.9*	15	41.7	20	40.9
	TT	16	34.8	17	47.2	22	44.9
IL-6 (C-174G) ***rs 1800795***	CC	5	10.9	3	8.3	9	18.4
	CG	26	56.5	24	66.7	27	55.1
	GG	15	32.6	9	25.0	13	26.5
IL-10 (592C>A) ***rs 1800872***	AA	21	45.6	19	52.8	32	65.3
	AC	20	43.5	13	36.1	16	32.7
	CC	5	10.9	4	11.1	1	2.0
IL-10 (C-819T) ***rs 1800871***	CC	30	65.2*	18	50.0	22	44.9
	CT	13	28.3*	16	44.4	27	55.1
	TT	3	6.5	2	5.6	-	-
IL-10 (G-1082A) ***rs 1800896***	AA	9	19.6	17	47.2**	3	6.1
	AG	26	56.5**	19	52.8*	43	87.8
	GG	11	23.9*	-	-	3	6.1

Note: * ≤0.05, * * ≤0.01 – comparing patients with IBS and ACPs and control group of healthy persons.

To detect possible genetic predisposition to disorders of reparative processes, the appearance of dysbiotic changes in patients with IBS and ACPs, we analyzed the detected SNPs in MMP 9 (A-8202G), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) genes (table 2).

Table 2

Features of SNP in MMP 9 (A-8202G), Tlr2 (Thr399ile), Tlr4 (Thr399ile), Tlr4 (Asp299Gly) genes in patients with IBS and ACPs

SNP of genes		IBS (n=46)		ACPs (n=36)		Control (n=49)	
gene	type	n	%	n	%	n	%
MMP 9 (A-8202G) ***rs 11697325***	AA	9	19.6	9	25.0	5	10.2
	AG	30	65.2	16	44.4*	38	77.6
	GG	7	16.2	11	30.6	6	12.2
Tlr2 (Thr399 ile) ***rs 5743708***	AA	36	78.3	28	77.8	48	97.9*
	AG	8	17.3	8	22.2**	1	2.1
	GG	2	4.4	-	-	-	-
Tlr4 (Thr399 ile) ***rs 4986791***	CC	36	78.3	26	72.2	31	63.3
	CT	10	21.7	10	27.8	16	32.7
	TT	-	-	-	-	2	4.0
Tlr4 (Asp299 Gly) ***rs 4986790***	AA	34	73.9*	27	75.0**	12	24.5
	AG	10	21.7**	5	13.9**	37	75.5
	GG	2	4.4	4	11.1	-	-

Note: * ≤0.05, * * ≤0.01 – comparing patients with IBS and ACPs and control group of healthy persons.

According to the presented data, heterozygous SNP of the MMP 9 gene was found in 16 (44.4 %) patients ($p<0.05$) and homozygous SNP was detected unreliable more often – in 11 (30.6 %) patients with ACPs. This confirms the more significant influence of this SNP on the development and course of the disease, affecting the disorders in the regulation of inflammation and reparation in CM.

Among the SNPs of Toll-receptor genes, the wild Tlr2 gene (rs 5743708) was found significantly less frequently in ACPs – 28 (77.8 %) patients and in IBS – 36 (78.3 %) patients ($p<0.05$), comparing with a control group. Heterozygous SNP of the Tlr2 gene (rs 5743708) was found in patients more often,

significantly at ACPs – 8 (22.2 %) patients (p <0.05), comparing with healthy individuals. Homozygous SNP of the Tlr2 gene (rs 5743708) was not found in all groups except patients with IBS – in 2 (4.4 %) patients. Homozygous SNP of the Tlr4 gene (Thr399ile) was detected only in 2 (4.0 %) people in the control group, which may be due to the peculiarities of the patients' population. The wild-type SNP of Tlr4 (rs4986790) gene was significantly more often found both in IBS – 34 cases (73.9 %) and ACPs – 27 (75.0 %) patients, compared with the control group (p<0.01). Heterozygous SNP of this gene was significantly less common in both groups, compared with healthy individuals – 37 (75.5 %) patients (p<0.01), which may be a unifying factor in these groups and may affect the appearance of polyps against the background of IBS. Homozygous SNP of the Tlr4 (rs4986790) gene was found in single cases with IBS and ACPs.

Given the importance of regenerative and reparative processes, DNA stability, proliferative changes and apoptosis in the ACPs development and their possible impact on disease progression and the appearance of neoplastic transformations in patients with IBS who have microinflammation in the CM, we studied the frequency of SNP detection in TgFb1 (Arg25Pro), CHEK2 (ile157Thr), Tp53 (Pro72Arg) Tp53 (pro47ser), Timp 1 (C536T) genes (table 3).

Table 3

Features of SNP detection of the TgFb1 (Arg25Pro), CHEK2 (ile157Thr) and Tp53 (Pro72Arg) genes in patients with IBS and ACPs

SNP of genes		IBS (n=46)		ACPs (n=36)		Control (n=49)	
gene	type	n	%	n	%	n	%
TgFb1 (Arg25Pro) ***rs 1800471***	CC	24	52.2**	23	63.9*	45	91.8
	CG	22	47.8**	13	36.1**	4	8.2
	GG	-	-	-	-	-	-
Tp53 (Pro72Arg) ***rs 1042522***	CC	7	16.2	4	11.1	5	10.2
	CG	23	50.0	12	33.3	19	38.8
	GG	16	34.8	20	55.6	25	51.0
CHEK2 (ile157Thr) ***rs 17879961***	CC	17	37.0**	20	55.6	35	71.5
	CT	14	30.4	15	41.7	13	26.5
	TT	15	32.6**	1	2.7	1	2.0

Note: * ≤0.05, * * ≤0.01 – comparing patients with IBS and ACPs and control group of healthy persons.

According to the presented data, the wild type of SNP of the TgFb1 (Arg25Pro) gene was detected less frequently in the group of IBS – 24 (52.2 %) patients (p<0.01) and in ACPs – 23 (63.9 %) patients (p<0.05), compared to the control group. Heterozygous SNP of the TgFb1 gene was detected more frequently both in the group of IBS – 22 (47.6 %) patients (p<0.01) and in ACPs – 13 (36.1 %) patients (p<0.01), compared to healthy individuals. This may indicate the similarity of hereditary mechanisms of influence on the disease occurrence and may be the cause of organic changes in patients with IBS and deeper disorders of the CM in ACPs. Wild, heterozygous and homozygous variants of SNP of the Tp53 (Pro72Arg) gene were found in all groups, with no significant difference. The wild SNP type of the CHEK2 gene (ile157Thr) was found significantly less frequently in patients with IBS – 17 (37.0 %) patients (p<0.01), the homozygous SNP type was more common – 15 (32.6 %) cases (p<0.01), which may confirm the connection of this SNP with the development of IBS and is a prognostic marker of the appearance of dysplastic changes in the CM. Heterozygous SNPs of the CHEK2 gene (ile157Thr) are insignificantly more frequently detected in patients with ACPs, compared with patients with IBS and healthy individuals. Since only wild-type SNP of Tp 53 (rs1800371) and Timp 1 (rs 11551797) genes were detected in all examined patients, SNP data were not considered as triggers of disease development.

According to our data, the SNP influence of genes on the development of IBS and ACPs was confirmed, which corresponds to the data of other researchers [2, 7, 15]. In addition, studied SNPs combined these diseases, which is crucial in the relationship between IBS and ACPs. The possible influence of SNPs responsible for cytokine stability on the development and course of IBS and ACPs has been proved, which corresponds to the data of foreign authors [2, 8]. Thus, IBS disease was associated with wild-type SNPs of the IL-10 gene (rs1800871), homozygous SNPs of the IL-10 gene (rs1800896), and SNPs of the IL-1 gene (rs 16944) (p<0.05). The wild-type SNP of the IL-10 gene (rs1800896) (p<0.01) had a significant effect on ACPs, which can determine the relationship between these diseases in the detection of a significant increase in the heterozygous SNP on the background of both IBS and ACPs (p<0.05). Among SNPs that directly regulate immune and inflammatory responses and affect the intestinal microbiota, the association of ACPs with SNP of the MMP 9 gene (rs11697325) was found (p<0.05). We identified the association of wild and homozygous variants SNP of CHEK2 (rs 17879961) gene in patients with IBS with the disease development, which can be considered as one of the possible prognostic markers of dysplastic changes in the CM on the background of functional disease.

The detection of increased content of wild and heterozygous SNP variants of gene Tlr2 (rs 5743708) ($p<0.05$) is a confirmation of the similarity of mechanisms of influence on IBS and ACPs. In addition, an increase in the frequency of the wild-type SNP variant of the Tlr4 gene (rs4986790), the appearance of homozygous SNP, and a decrease in the heterozygous SNP variant were found in both groups compared with healthy individuals. The similarity of the detected changes determined the possibility of the relationship between these diseases and the possible protective effect of SNP of Toll-like receptor's genes, which confirms the data of other researchers [14]. Detection of a decrease in the frequency of wild-type SNP of the TgFb1 gene (rs 1800471) in patients with IBS and ACPs in contrast to heterozygous SNP, which increased in both groups compared to healthy individuals ($p<0.01$), may be a unifying factor and indicate the general mechanisms of the course and possible neoplastic transformation on the background of functional disease.

Conclusion

Thus, the obtained data confirmed the SNP influence on the development, course and possible relationship of IBS and ACPs. The association of the wild SNP variant of the IL-10 gene (rs1800871), the homozygous SNP of the IL-10 gene (rs1800896), the heterozygous SNP type of the IL-1 gene (rs 16944), and the wild and homozygous SNP variants of the CHEK2 gene (rs 17879961) was determine with IBS development. The wild-type SNP of the IL-10 gene (rs1800896) and the heterozygous SNP variant of the MMP 9 gene (rs11697325) had a significant effect on ACPs. The overall effect and relationship for patients with IBS and ACPs was determined by SNPs of the TLr2 (rs 5743708), Tlr4 (rs4986790), and TgFb1 (rs 1800471) genes. Timely determination of SNP data in patients with IBS and ACPs will help identify the predisposition to the appearance and progression of organic diseases, will prevent neoplastic transformation, modifying the lifestyle of patients and prescribing treatment in a timely manner.

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