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Molecular genetic diagnosis of inflammatory bowel diseases

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Abstract . Inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), despite the development of modern, high-tech methods of diagnosis and treatment, in almost all countries maintain or acquire a tendency to increase the prevalence and incidence, especially among persons young and working age (Kaplan G.G., 2015; Ng S.C. et al., 2018). At the same time, the lack of an unambiguous understanding of the causes and mechanisms of IBD development makes it difficult to establish a diagnosis of CD or UC in a timely manner, which, in some cases, leads to the development of severe complications requiring surgical intervention and an unfavorable medical and social prognosis (Zhang Y.Z. et al., 2014; de Lange K.M. et al., 2015). In addition, the similarity of clinical, endoscopic and laboratory signs of CD and UC makes it difficult to carry out their differential diagnosis, as well as individual prediction of the clinical course of diseases and the correct choice of treatment tactics (Dulai P.S. et al., 2018). This, in turn, determines the need for improvement of traditional diagnostic algorithms for IBD using laboratory biomarkers that have clinical, pathogenetic, diagnostic and prognostic significance in CD and UC. Certain prospects for improving the efficiency of diagnostics and predicting the risk of developing IBD appeared after deciphering the human genome Gene polymorphisms associated with the clinical implementation of key links in the pathogenesis of CD and UC, in particular, disorders of innate and adaptive immunity, differentiation of Th17-lymphocytes, intestinal mucosal and epithelial barriers, and autophagy, have been identified (Zhang J.X. et al., 2014; Aamann L. et al., 2014; Cheng Y. et al. 2015). However, the available data on the features of the clinical implementation of genetic factors associated with the development of IBD, obtained in different countries and even in different regions within the same country, are very contradictory (LeeG.H.etal., 2005; Valuyskikh E.Yu., 2008; Chua K. H. et al., 2009; Shumilov P. V., 2010; Nasykhova Yu. A. et al., 2010; Liu J. Z.et al., 2015), which hinders the introduction of molecular genetic methods for diagnosing CD and UC into clinical practice. Perhaps this is due to the different prevalence of the studied polymorphisms, as well as the peculiarities of their clinical implementation in various combinations with individual environmental factors.

Keywords: CARD15 gene, polymorphism, genetic testing, prognosis, Crohn's disease, ulcerative colitis

Introduction.For the first time in the decades of the 21st century, there has been a progressive increase in the prevalence of inflammatory bowel diseases (IBD) throughout the world, to a greater extent in developed countries and among the young working population [1]. At the same time, there is still no clear and unambiguous

idea of the pathogenesis, effective methods of early diagnosis and prediction of the risk of development and features of the clinical course of Crohn's disease (CD) and ulcerative colitis (UC). Insufficiently informative for early diagnosis, differential diagnosis or prediction of the development of IBD and such instrumental methods as ultrasound, computed tomography and magnetic resonance imaging [2]. In recent years, the determination of serological biomarkers, perinuclear antineutrophil cytoplasmic antibodies (pANCA) and antibodies to baker's yeast Saccharomyces cerevisiae (ASCA) [5], has been introduced into the clinical practice of gastroenterological departments [5], but this did not contribute to any significant improvement in the early diagnosis of CD and UC, prognosis features of their clinical course and the effectiveness of the therapy. A fundamentally new approach to the development of methods for early diagnosis and prediction of the development of IBD emerged after the decoding of the human genome and the subsequent rapid development of functional and clinical genomics. More than 1500 nucleotide polymorphisms of genes have been identified (CARD15, TLR2, TLR4, TLR9, CARD9, TNF-α, TNFRSF1A, TNFRSF1B, IL-10, IL-4, MST1, IL-18RAP, TGFB1, IL-23R, STAT3, JAK2, IL-12 DEFB1, VDR, TFF1-3, MUC2, MUC3, MUC4, ATG16L1, IRGM, CALCOCO2/NDP52, etc.) associated with various links in the pathogenesis of CD and UC, the features of their clinical course and response to therapy [7]. In particular, it was found that out of more than 60 polymorphisms of the CARD15 (NOD2) gene, the G2722C (rs2066845) and 3020insC (rs5743293) polymorphisms have the greatest diagnostic and prognostic significance in the development of CD [8].

According to current domestic and foreign literature, ulcerative colitis is an inflammatory bowel disease, in the development of which, as in Crohn's disease, defects in congenital and acquired immunity, disorders of the intestinal microflora, environmental factors against the background of genetic predisposition [1; 2]. However, the question of the etiology of the disease is still open. The significance of the vascular endothelium in the development of ulcerative colitis has been less studied [10]. In patients with ulcerative colitis, an immunohistochemical study revealed an increased density of microvessels in the colon tissue, which correlated with the degree of disease activity and the expression of vascular endothelial growth factor [11].), interleukin-6 (IL6) and vascular endothelial growth factor (VEGFA). Modern research shows the important role of hereditary factors and response to treatment in a number of diseases. This stimulated a series of studies to identify the association of IBD with certain gene loci [1–3, 5, 6]. Of particular interest is the understanding of the ways in which genetic factors are realized in IBD and what are the features of the clinic, depending on the genetic status of the patient. In this regard, the NOD2/CARD15 and TNF-α genes are of the greatest interest. The NOD2 (nucleotide-binding oligomerization domain containing 2) or CARD15 (caspase recruitment domain family, member 15) gene (16q12) is responsible for the

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activation of the nuclear factor that regulates the expression of pro-inflammatory cytokines and the body's response to the bacterial polysaccharide [4]. Three polymorphic variants of the gene associated with the development of inflammatory bowel diseases have been identified [1]: Arg702Trp, Gly908Arg, Leu3020insC. The second gene, TNFα (tumor necrosis factor α), encodes a pro-inflammatory cytokine that plays an important role in the pathogenesis of ulcerative colitis, in particular, in the development of an inflammatory response [3]. wo polymorphic variants of the gene have been identified: -238G/A and -308G/A, which have opposite effects on protein production - the replacement of G with A at position -308 significantly increases the transcriptional activity of the gene, and at position -238, on the contrary, reduces the synthesis of TNFα. There are data on the association of the -308G/A polymorphism with the age of onset, the severity of the course, and the frequency of recurrence of the disease [1, 3]. In recent years, there has been an increase in interest in the study of genetic determinants of the development and progression of the disease and response to drug therapy. Among the most widely studied genetic factors are single nucleotide polymorphisms (Single Nucleotide Polymorphism, SNP), which are associated with point substitutions or microdeletions and insertions in the genome [2, 4]. It is believed that the presence of single nucleotide substitutions is one of the factors that determine the individual characteristics of the course of the disease, and their detection can be used to determine the prognosis of the disease. Currently, the study of the “functional (responsible for altered production) gene polymorphism” of cytokines and their receptors is of great interest, since these mediators make the greatest contribution to the regulation of immunity [7]. The expression of cytokine genes begins in response to antigenic irritation or tissue damage. With UC, there is an increased production of cytokines - interleukin 1β (IL 1β), IL 5, IL 6, IL 8, IL 13, IL 17, IL 22, tumor necrosis factor α (TNFα), TL1A. Data on the effect of polymorphism of genes encoding the synthesis of cytokines and their receptors are constantly updated, let us dwell on only one of them. Nevertheless, many doctors are very skeptical about genetic testing. This is consistent with the position of the European Crohn's and Colitis Organization (ECCO) and the American Gastroenterological Association (AGA), which do not recommend the use of genetic markers in the routine diagnosis and prognosis of the development of CD and UC [11 -14]. The main reason is the ambiguity and often contradictory data on the association of genetic factors with the development of IBD. Thus, the 3020insC and G2722C polymorphisms of the CARD15 gene in most countries of Europe and America are associated with the development of only CD, and in the Indian population also with the development of UC. Residents of Japan, China, and South Korea have virtually no associations of these polymorphisms with IBD [8–10, 15].

Conclusion. In the ECCO and AGA consensus documents on the diagnosis of IBD, the use of genotyping in clinical practice is not yet recommended due to insufficient evidence base, however, we consider it promising to further study the

prevalence and prognostic significance of the 3020insC and G2722C polymorphisms of the CARD15 gene, as well as other nucleotide polymorphisms associated with VZK. The information obtained in the course of such studies can be used to create international genetic databases on the population characteristics of the frequency of occurrence, pathogenetic, clinical diagnostic and prognostic significance of polymorphisms associated with IBD, which will further develop ways to increase the objectivity and information content of diagnosing and predicting the development of CD. and UC using molecular genetic technologies.

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