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Genetic and environment factors influencing Crohn's disease

Fan YH *et al.* Factors influencing Crohn's disease

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Abstract

This editorial discusses Raffaele Pellegrino's essay, which appeared in the most recent edition of the *World Journal of Gastrointestinal Surgery*. Crohn's disease (CD) is a complex and multifactorial disease that is influenced by a combination of genetic and environmental factors. While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as NOD2, smoking, and vitamin D. Understanding the interplay between genetic and environmental factors is crucial for developing effective strategies for preventing and treating this chronic inflammatory bowel disease.

Key Words: Crohn's disease; Pathogenesis; NOD2; Smoking; Vitamin D

Core Tip: The link and complicated mechanisms between CD, NOD2 (nucleotide-binding oligomerization domain-2), smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of

individual therapy. Individualized treatment, including surgery and medications, is important.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that affects millions of individuals worldwide[1]. This debilitating condition is characterized by inflammation of the lining of the digestive tract, leading to a range of symptoms including abdominal pain, diarrhea, weight loss, and fatigue[2]. The exact cause of CD remains unknown, but it is believed to result from a complex interplay of genetic, environmental, and immune factors[3]. About 60%-70% of CD patients may experience complications such as abdominal abscess, intestinal obstruction, intestinal perforation, intestinal fistula, intestinal leakage, and gastrointestinal bleeding in the later stage, requiring one or even multiple surgical treatments[4]. A key feature of CD is dysregulation of the immune response, with an exaggerated inflammatory response to intestinal bacteria believed to play a central role in the development of the disease[5]. Genetic factors also contribute to the risk of developing CD, with certain genetic variations known to increase susceptibility to this condition[6]. Environmental factors such as diet, smoking, and the composition of the gut microbiota are also thought to play a role in triggering or exacerbating inflammation in individuals predisposed to CD[7]. The colonic bacterial composition in CD is altered compared to healthy individuals, and this dysbiosis, an imbalance in the microbial community, appears to contribute to both the onset and the exacerbation of inflammation in the gut. Table 1 summarized the potential factors influencing CD.

GENETIC FACTORS

Genetic factors have long been recognized as playing a key role in the development of CD. In fact, having a first-degree relative with CD can increase the risk of developing the disease by up to 20 times. Variants in the nucleotide-binding oligomerization

domain-2 (NOD2) gene, involved in the immune response to bacteria in the gut, could increase risk of developing CD.

NOD2 mutations are associated with some phenotypes of CD, such as fibrous stenosis or penetrating lesions[8]. NOD2 gene deficiency leads to intestinal inflammatory gene expression and dysfunction of goblet cells in the intestinal mucosa in mice. These abnormalities are related to excessive production of kinesin by intestinal mucosal intraepithelial lymphocytes. In addition, scholars also detected an increase in the number of pro-inflammatory microorganisms Bacteroides in the gut. The mice with NOD2 mutation have autophagy dysfunction and increased bacterial lipopolysaccharide, which leads to the activation of Toll like receptors, the massive release of a variety of inflammatory related factors and the waterfall like effect, and finally causes intestinal inflammatory response[9].

The identification of these genetic risk factors has helped to improve our understanding of the underlying mechanisms that drive the development of CD. For example, studies have shown that mutations in the NOD2 gene can lead to an abnormal immune response in the gut, leading to inflammation and damage to the intestinal lining. Other genetic variants have been linked to abnormalities in the gut microbiome, the community of bacteria that live in the intestines and play a crucial role in regulating the immune system.

GENETIC VARIANTS TO IMPROVE THE EFFECTIVENESS OF DIAGNOSIS AND TREATMENT

Over the last few decades, CD-associated genetic variants largely affect immune responses, intestinal barrier function, and microbial interactions. Variants in the IL23R gene, which play a crucial role in the regulation of T-cell responses, are also strongly associated with CD. The involvement of IL23R in immune cell regulation suggests a potential therapeutic target. ATG16 L1 and IRGM are involved in autophagy, a process critical for the immune response to pathogens. Mutations in these genes can lead to impaired autophagy and contribute to CD pathogenesis. Variants in TNFSF15 (TNF

Superfamily Member 15) have been linked to an increased risk of CD, particularly in European and Asian populations, suggesting a role in the regulation of inflammation. While genetic testing for CD is not yet routine in clinical practice, it holds potential in early diagnosis. Identifying patients at high genetic risk could enable earlier intervention, potentially altering the disease course. Moreover, genetic variants such as those affecting drug metabolism can influence a patient's response to medications and their risk of adverse effects.

ENVIRONMENT FACTORS

Several environmental risk factors have been identified, including smoking, diet, and stress. Smoking is one of the most well-established environmental risk factors for CD, with smokers being twice as likely to develop the disease compared to non-smokers. Studies have shown that smoking can disrupt the balance of bacteria in the gut and increase inflammation, contributing to the development of CD.

Smoking as one environmental factor has long been recognized as a risk factor for several health conditions, including heart disease, lung cancer, and respiratory problems. Recently, smoking has been of particular interest in relation to CD. Several studies have suggested that smoking may have a significant impact on the development and progression of CD[10, 11]. For instance, research has shown that smoking can increase the risk of developing CD in individuals with a genetic predisposition to the condition[12]. Additionally, smokers with CD may experience more severe symptoms, require more aggressive treatment, and have a higher risk of complications compared to non-smokers with the condition. Chronic smokers, particularly those who have smoked for many years, are at an increased risk of developing CD, with studies indicating that smoking may accelerate disease onset and increase the severity of symptoms. Smoking duration and intensity are important factors in modulating disease outcomes, with heavy smokers experiencing more frequent flare-ups and complications compared to non-smokers. Both active smoking and passive exposure to tobacco smoke have been associated with increased disease risk. However, the risk is significantly higher in active

smokers. While the exact mechanisms remain unclear, smoking-induced changes in the gut's immune system and microbiota ² are believed to play a key role in the pathogenesis of CD.

Diet is another important environmental factor that can influence the development of CD. Research has shown that ⁶ a diet high in processed foods, sugar, and saturated fats can increase inflammation in the gut and disrupt the balance of bacteria, contributing to the development of the disease. In contrast, a diet high in fruits, vegetables, and fiber has been shown to reduce inflammation and promote a healthy gut microbiome, reducing the risk of developing CD.

Vitamin D plays an important role in the pathogenesis by participating in the regulation of intestinal immune function^[13]. Most patients with CD are complicated with vitamin D deficiency, and the reduction of vitamin D is significantly correlated with the incidence of CD^[14]. 1,25-dihydroxyvitamin D₃ can significantly increase the secretion of antimicrobial peptides by Paneth cells in the intestinal mucosa through binding with vitamin D receptor, and promote the development and differentiation of regulatory T cells and type 2 helper T cells^[15]. Vitamin D also affects the function of natural killer T cells and reduces the production of related cytokines such as Th17 cells. In addition, vitamin D can protect patients with CD by increasing the number and abundance of beneficial bacteria and regulating the polymorphism of bacteria in the gut^[16]. And vitamin D supplementation can reduce the recurrence rate of CD. The threshold for vitamin D deficiency commonly used in clinical practice is typically below 20 ng/mL (50 nmol/L), which is consistent with the definition of deficiency from organizations like the Institute of Medicine (IOM) and the Endocrine Society. Levels between ⁵ 20–30 ng/mL are considered insufficient, while levels above 30 ng/mL are generally considered sufficient for bone and immune health. Most studies implicating vitamin D in Crohn's disease have linked deficiency levels (under 20 ng/mL) with poorer disease outcomes, such as higher disease activity, increased flare-ups, and poorer response to treatment. Vitamin D deficiency may be associated with the development of CD^[17].

There are also some other environmental factors such as smoking e-cigarettes, exposure to various food toxicants, *etc.* The use of e-cigarettes is increasingly common, and while it is considered less harmful than traditional smoking, emerging evidence suggests it may still have a detrimental effect on gut health. E-cigarette vapors contain various chemicals, such as nicotine, formaldehyde, and acrolein, which can alter the gut microbiota, increase oxidative stress, and trigger inflammatory responses. Nicotine, in particular, may exacerbate CD by promoting Th17-mediated inflammation and impairing mucosal immunity. The long-term effects of vaping on CD are not fully understood but may include the potential to exacerbate existing disease or trigger the onset in susceptible individuals. ⁷ Exposure to environmental pollutants, including particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and ozone (O₃), has been associated with an increased risk of inflammatory bowel diseases, including Crohn's disease. These pollutants can promote systemic inflammation, affect the gut immune response, and disrupt the microbiome.

EFFECT OF UNHEALTHY DIET, AND LIFESTYLE

Diets high in sugar, processed foods, and refined carbohydrates (*e.g.*, white bread, sugary drinks, and sweets) have been shown to promote inflammation in the body. These foods can trigger or worsen flare-ups of CD by aggravating the gut's immune response. Diets rich in unhealthy fats, particularly trans fats and saturated fats, have been linked to increased intestinal inflammation. Excess fat intake can promote the production of pro-inflammatory cytokines, which increase gut inflammation and can contribute to the severity of Crohn's symptoms.

CLINICAL IMPLICATIONS

Despite these findings, the link between CD, NOD2, smoking, and vitamin D is complex and poorly understood. In addition to genetic and environmental factors, the interaction between the two is also thought to play a role in the development of CD. Similarly, environmental factors may influence the expression of certain genes that

increase the risk of developing the disease. Furthermore, the consequences of CD differ from person to person, emphasizing the importance of individual therapy. The complicated mechanisms underlying the link between CD, NOD2, smoking, and vitamin D need to be studied further for therapeutic applications. Individualized management, including surgery and medicines, is significant[18].

CONCLUSION

1 While genetic factors play a key role in the development of the disease, environmental factors also play a significant role in influencing the risk of developing CD. By looking at present understanding of CD pathogenesis, we emphasize the important factors involved in the development of this illness, such as NOD2, smoking, and vitamin D. 1 Understanding the interplay between genetic and environmental factors is crucial for preventing and treating this chronic inflammatory bowel disease.

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