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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Molecular basis of the irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain, discomfort and bloating. The pathophysiology of IBS is poorly understood, but the presence of psychosocial basis is now known. There is an increasing number of publications supporting the role of genetics in IBS. Most of the variations are found in genes associated with the brain-gut axis, revealing the strong correlation of brain-gut axis and IBS. miRNAs, which play critical roles in physiological processes, are not well studied in IBS. However, so far there is found an involvement of alterations in miRNA expression or sequence, in IBS symptoms. IBS phenotype is affected by epigenetic alteration and environment. Changes in DNA and histone methylation are observed in patients who suffered childhood trauma or abuse, resulting in altered gene expression, such as the glucocorticoid receptor gene. Finally, diet is another factor associated with IBS, which may contribute to symptom onset. Certain foods may affect on bacterial metabolism and epigenetic modifications, predisposing to IBS.

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Key words: Irritable bowel syndrome; Gastrointestinal diseases; Genetics; Epigenetics; Diet

Core tip: Irritable bowel syndrome (IBS) is a multifactorial disease, whose development and phenotype are related to both genetic and epigenetic factors. Gene polymorphisms and epigenetic modifications affect the function of brain-gut axis and are responsible for many of the symptoms of the disease. The relationship between environmental factors and IBS shows the effect of environment on gene expression alteration by epigenetic modification.

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INTRODUCTION

Irritable bowel syndrome (IBS) is amongst the most widely recognized functional gastrointestinal disorders and is remarkably prevalent in the general population, affecting as many as 5%-20% of people worldwide[1]. The prevalence of IBS is slightly higher in women, with a variable influence of age across studies. Symptom based criteria is applied to diagnose the entity. The presence of chronic or recurrent abdominal pain or discomfort, relieved by defecation and associated with an altered bowel habit, in the absence of any underlying structural or bio-

Table 1 Genetic alterations on irritable bowel syndrome

Gene	Polymorphism	Ref.
Serotonergic system		
SERT promoter	5-HTTLPR, deletion	[13-17]
	rs25531	[81]
HTR3A	-42C > T	[50]
HTR3B	386A > C	[82]
HTR3C	489C > A	[83]
HTR3E	rs62625044	[50]
Adrenergic and opioidergic system		
α_2-adrenergic receptor	α2C del 322-325, deletion	[19]
	α2A-1291C > G	[19,84]
COMT	α2A-1291 C > G	[20]
	$Val^{158}Met$	[21,22]
CNR1	(AAT)n triplet repeat	[23]
	rs806378	[24]
CRH-R1	rs7209436	[27]
	rs242924	[27]
BDNF	$Val^{166}Met$	[85]
OPRM1	118A > G	[85]
Cytokines		
IL-10	-1082 A > G	[28-30]
	396 T > G	[30]
	-819T > G	[34]
TNF alpha	-308G > A	[28]
	-238G > A	[86]
GNβ3	825C > T	[32]
TLR9$^+$	-1237T > C	[84]
	2848 G> A	[84]
IL1R	Pst- I 1970C > T	[86]
IL4	-590C > T	[84,87]
	-33T	[87]
IL6	-174G > C	[84,86]

SERT: Serotonin reuptake transporter; COMT: Catechol-*O*-methyltransferase; CNR1: Cannabinoid receptor 1; CRH-R1: CRH receptor 1; IL: Interleukin; TNF: Tumor necrosis factor.

chemical abnormalities, identifies patients with IBS[2].

The syndrome has been subdivided into different subgroups based on the predominant bowel habit; diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), or a mixture of both diarrhea and constipation (M-IBS). The use of these subgroups has received acceptance by most clinical investigators, as it commonly dictates symptomatic pharmacological management[3]. However, the value of this categorization is under consideration, knowing that each IBS patient could switch from one subgroup to another over time.

There is a significant variability in the clinical presentation of patients with IBS and they could differ by predominant stool type, severity and frequency of pain/discomfort and comorbidities including psychological distress and somatic complaints[4]. Moreover, IBS symptoms can fluctuate over time. The severity and intensity of IBS symptoms vary from very mild in patients who do not seek medical attention to very severe one that may significantly affect quality of life with the same degree of impairment as major chronic disorders. Despite the fact that a minority of IBS patients chooses to consult a physician, IBS is a clinical problem of considerable cost for the health care system because of its high prevalence and the chronic or recurrent nature of symptoms[5].

The pathophysiology of IBS is largely unknown and it is generally considered a multifactorial disorder. Among the putative mechanisms involved in the pathogenesis of IBS, there is evidence to support the key role of heritability and genetics factors. It is recognized that psychological factors and stress appear to be the primary drivers of symptoms in IBS patients. There is a hypothesis that IBS patients have a certain personality with predisposition to develop the disease. Dimensions of personality that are important in clinical practice include response to stress, attitude toward illness, health and medical treatment. These constitutional features may have genetic origins that may be influenced by early environmental experiences.

GENETICS AND IBS

Gene polymorphisms

IBS, as a multifactorial disorder, is also associated with altered brain-gut axis[6]. A recent study showed that corticotrophin-releasing hormone (CRH) is involved in stress-related pathophysiology of IBS and in the inflammation of the intestinal mucosa[7]. Polymorphisms in genetic factors may influence these mechanisms, and affect brain-gut interrelations[8-10]. Polymorphisms involve the serotonergic, adrenergic and opioidergic systems, and genes encoding proteins with immunomodulatory and/or neuromodulatory features[9,10].

Serotonergic system

Serotonin [5-hydroxytryptamine (5-HT)] controls gastrointestinal secretion, motility, and visceral perception by activating at least five types of receptors[10]. Alterations in 5-HT levels and signaling are present in IBS patients which may induce diarrhea, nausea, and vomiting[11,12]. So far, only a few gene polymorphisms are associated with IBS. Polymorphisms in promoter of serotonin reuptake transporter (*SERT*) gene effect on transcription activity and influence 5-HT reuptake efficiency. In a recent study, among 9 polymorphisms in promoter region of SERT, only one polymorphism (insertion/deletion polymorphism) was associated with diarrhea in women with IBS. The deletion polymorphism decreases expression of the sodium-dependent serotonin transporter and, thus, reduces reuptake of serotonin[13]. Another study showed a lower prevalence of the SS genotype (homozygosity for deletion) in IBS and, particularly, in D-IBS, but this was only observed in male patients[14] (Table 1).

This polymorphism is also correlated with behavioral traits and psychiatric disorders and IBS patients homozygous for the deletion present significantly higher risk for depressive episodes[15]. Another study also associated insersion/deletion polymorphism with anxiety. Long allele (insertion) in females is implicated with negative emotion but acts contrary in males[16]. This allele influences the efficacy of tegaserod treatment. IBS patients

carrying the long allele respond poorly to treatment[17].

Adrenergic and opioidergic systems

Autonomic system has an important role in gastrointestinal motility, acting *via* adrenergic receptors. Genetic variations in α_2-adrenergic receptor may change sensory and motor function in IBS[18]. α2C Del 322-325 deletion, a variation resulting in a loss-of-function phenotype, is associated with C-IBS (constipation IBS)[19]. The α2A -1291 C>G is associated with D-IBS, but no with C-IBS[20] (Table 1).

A polymorphism (Val^{158}Met) in catechol-*O*-methyltransferase, an enzyme metabolizing catecholamines, showed association with IBS[21]. Patients carrying this polymorphism have a reduced response to pain[22] (Table 1).

Alterations in cannabinoid receptor genes are also analysed and associated with IBS. A polymorphic (AAT)n triplet repeat in the 3-flanking region of the cannabinoid receptor 1 (*CNR1*) gene is related with IBS and severity of abdominal pain in IBS[23] (Table 1).

Additionally, single nucleotide polymorphisms (SNPs) in CRH receptor 1 (CRH-R1), which plays a critical role in stress-induced pathophysiology of IBS, were studied for moderating IBS phenotype and negative emotion in IBS patients (Table 1). Findings of this study showed association between SNPs and IBS moderation, but no association was found with negative emotion[24]. Genetic variation rs806378 in CNR1 is associated with colonic transit in D-IBS and sensation rating of gas[25] (Table 1). This polymorphism is also correlated with treatment effectiveness of nonselective cannabinoid receptor agonist, dronabinol[26,27].

Cytokines

Several studies have reported cytokine gene polymorphisms in IBS. Interleukin (IL)-10-1082 G/G, a high producer IL-10 genotype, correlated with lower risk for developing IBS[28,29] (Table 1). Gene SNPs of IL-8 and IL-10 were also analyzed by Romero-Valdovinos *et al*[30] and an association between alleles IL-8$^+$ 396G and IL-10-1082A and IBS was found. These findings were confirmed by other study[31] (Table 1). TNF alpha (-308 G/A) polymorphism and IBS are correlated, and G/G genotype may increase risk of IBS. G/A genotype has a protective role[28] (Table 1). A study evaluating GNβ3 825C>T polymorphism in IBS showed significant interactions between gastrointestinal infection and T allele in the development of IBS, suggesting gene-environment interactions[32] (Table 1). However, another study replicated none of these results[33]. Another IL-10 polymorphism associated with IBS is IL-10-819 T>C. The frequency of IL-10 -819 CC genotype was significantly higher in D-IBS[34] (Table 1).

miRNAs and IBS

miRNAs are small (21-23 nucleotides) single-stranded RNA molecules[35,36]. miRNAs are not translated into proteins and have regulatory function, such as translational repression of targeted mRNAs[37]. miRNAs form RNA-induced silencing complex, which can prevent the expression of proteins, either by activating endonuclease that degrades mRNAs or by blocking translation[38]. miRNAs are connected with physiological processes such as cell division and death[39], cellular metabolism[40], intracellular signaling[41], immunity[42] and cell movement[43]. Thus, altered miRNA expression can affect these critical processes, and as a result, lead to various pathological and occasionally malignant outcomes.

Cancer is one of human diseases clearly associated with miRNA regulation. miRNAs may involve in tumor development as tumor suppressors or oncogenes. They also play roles in tumor invasion and metastasis. Down-regulation of miR-15 and miR-16 is correlated with the pathogenesis of B-cell chronic lymphocytic leukemia[44]. In addition, miR-125b, miR-145, miR-21 and miR-155 expression is associated with the increased risk of breast cancer[45]. The implication of miRNAs in immune-related diseases, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), and type I / II diabetes is also known. In MS, miR-34a, miR-155 and miR-326 are overexpressed[46]. In SLE, increased risk of disease development is associated with decreased expression of miR-46a[47]. Several studies show that miRNAs regulate critical pathways in inflammation, such as pathways correlated with nuclear factor kappa beta. miR-155 and miR-146 are the best characterized miRNAs which are implicated in immune-diseases[46,48,49].

The role of miRNAs in IBS is not well studied. The first association of miRNAs and IBS was from Kapeller *et al*[50]. This study showed that the variation c.*76G>A (rs62625044) in the 3' untranslated region (UTR) of the serotonin receptor type 3 subunit genes *HTR3E* correlates with D-IBS. This functional variation is located in the miRNA-510 target site of the gene. The co-localization of HTR3E and miR-510 in enterocytes of the gut epithelium and the presence of cis-regulatory variation show the regulation of serotonin receptor gene expression by miRNA.

Next evidence came from Zhou *et al*[51], who evaluated the miRNA expression in blood microvesicles (circular membrane fragments that are shed from the cell surfaces and accompanies cell activation) and gut tissues in D-IBS patients and IBS patients with normal membrane permeability. They found that miR-29a expression was increased in blood microvesicles in the small bowel and colon tissues of IBS patients with increased permeability. miR-29a is complementary in the 3' UTR of the glutamine synthetase gene. These results suggest the role of glutamine synthetase in the intestinal membrane permeability and the role of miR-29a in regulation of glutamine synthetase and intestinal membrane permeability.

EPIGENETICS AND IBS

Phenotype is the combination of DNA sequence, epigenetic DNA modifications and environmental factors.

The presence of epigenetic changes in monozygotic twins, leading to phenotypic alterations, suggests a potential role of epigenetics in IBS[52]. DNA methylation and histone modification are the most common epigenetic mechanisms. DNA methylation usually silences gene expression[53]. However, histone acetylation or methylation may activate or not gene transcription[54].

IBS is associated with early life trauma or abuse, and this condition leads to negative health outcomes and behaviors in adults. Childhood trauma influences somatic symptoms and neural network development and neuroendocrine system development[55-57]. In a recent study, IBS patients showed enhanced cortisol response to a visceral stressor. The hypothalamic-pituitary-adrenal (HPA) axis hyperresponsiveness to stressor is more related to early adverse life events rather than to the presence of IBS[55].

Early childhood trauma decreases glucocorticoid receptor expression by hypermethylation of glucocorticoid receptor gene[58]. Altered glucocorticoid receptor gene expression, which mediates the negative feedback of the HPA axis, reduces the capability of HPA to deal effectively with stress. In animal model of IBS, animals exposed to perinatal stress had methylation of glucocorticoid receptor promoter, decreased gene expression and prolonged elevation of corticosterone levels[59].

The impact of early adverse life events on developing IBS or other diseases is being explored lately. Gluckman *et al*[60] developed a hypothesis that epigenetic processes, including DNA methylation and histone modification, partially mediate developmental plasticity. Another group searched for a mechanism that link the social environment early in life and long-term epigenetic programming of behavior and responsiveness to stress. They took into account data suggesting that DNA methylation is a dynamic process and postmitotic cells may change methylation pattern responding to different environmental stimuli. This study showed that maternal licking and grooming in the rat triggered activation of 5-HT receptors, activation of the transcription factor nerve growth factor-induced gene A and acetylation of the promoter of the glucocorticoid receptor (mediated by a histone acetyl transferase), leading to differential epigenetic programming of the glucocorticoid receptor[61].

Alterations in acetylation motif change behavior in adult offsprings. Except maternal care, diet may also affect behavioral plasticity[62]. Maternal separation acts as a stressor and helps adult rats to develop intestinal mucosal dysfunction, increased HPA axis responses and anxiety-like behavior[63].

Finally, early life stress increases the levels of proinflammatory cytokines. In IBS patients, levels of IL-6 and IL-8 were high, as a result of epigenetic glucocorticoid alterations[64,65]. Upregulation of proinflammatory cytokines influences tryptophan metabolism, resulting on changes of 5-HT activity[66]. The kynurenine:tryptophan ratio, which shows tryptophan catabolism, is increased in IBS patients with severe symptoms, and they were more likely to have depression or anxiety.

DIET, NUTRIGENOMICS/ NUTRIGENOMICS AND IBS

It is well documented, that the interplay between genes and diet may be reflected in susceptibility to various diseases[67]. Scientific studies have demonstrated the effectiveness of dietary therapies in alleviating the symptoms and even in altering the progression of inflammatory and autoimmune disorders[68,69]. Concerning the IBS, even if many patients recognize the impact of specific diet in symptom occurrence, limited population-based studies have evaluated the importance of diet in IBS and its role remains uncertain[70-72]. Diet may contribute to symptom onset through several mechanisms such as food allergy and intolerance. Additionally, certain food may alter the composition of the luminal milieu, directly or indirectly through effects on bacterial metabolism. Diet is known also to influence the epigenetic modification of genes[73]. Finally, IBS symptoms may develop following exposure to food-born pathogens[72]. Furthermore, an increase probability of developing IBS is associated with the inheritance of a number of contributory genetic polymorphisms, as well as with the altered expression of certain genes[74]. The variant forms of genes often result in an abnormal response to normal gut bacteria that may be changed through inappropriate diet or environment. Shifts in the bacterial makeup of the human gut microbiota have been associated with gut disorders including IBS[75]. In the field of nutritional research, 2 terms have been established: nutrigenomics which aims to study how genotype determines optimal dietary requirements for health on an individual basis, and nutrigenomics which studies the effect on diet on DNA structure and gene expression[76]. However, the most of the nutrigenetic/nutrigenomic work has focused on cardiovascular disease, type Ⅱ diabetes mellitus or inflammatory bowel disease[77,78] and no study has be done on IBS. Low FODMAPs diet, that is elimination of fermentable Oligo-, Di- and Mono-saccharides, and Polyols from diet, is an area of intense investigation for symptoms' alleviation[79,80]. FODMAPs' ingestion could result in the symptomatology of these patients, because they are osmotically active, they are fermented and through bacterial overgrowth can cause bloating, pain and the sequence of symptomatology in IBS. Thus, the application of these approaches in the field of IBS research is open. It is hoped that the nutrigenomics/nutrigenomics implementation will promote the understanding of diet-gene interactions and facilitate a better characterization of individual IBS patients for further identification of nutritional patterns that allow personalized therapies.

CONCLUSION

IBS is a multifactorial disease, whose development and phenotype are related to both genetic and epigenetic

factors. Most factors involve in pathogenesis by causing changes in gene expression. Gene polymorphisms and epigenetic modifications affect the function of brain-gut axis and are responsible for many of the symptoms of the disease. IBS is one of the diseases where the environmental influence is strong. Early life incidents and diet habits play an important role in disease development. The relationship between environmental factors and IBS shows the effect of environment on gene expression alteration by epigenetic modification.

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