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REVIEW

Genetic determination of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. According to the Rome Ⅲ criteria, IBS is defined as recurrent abdominal pain or discomfort for at least 3 d per month during the previous 3 mo associated with two or more of the following symptoms: improvement with defecation, onset associated with a change in the frequency of stool and/or onset associated with a change in form or appearance of stool. There is growing evidence regarding the genetic contribution in IBS, however the precise etiology of IBS is still unknown. The evaluation of the genetic influence is based on twin studies, familial aggregation and genetic epidemiological investigations. Most studies showed a concordance for IBS significantly greater in monozygotic than in dizygotic twins. The majority of the studies have shown that familial aggregation may represent exposures to a similar environment, as well as the influence of genetic factors. Whereas no specific gene has been identified in association with IBS, recent studies have noticed the importance of polymorphisms in the promoter region of the serotonin reuptake transporter gene, G-protein beta 3 subunit gene (*C825T*), cholecystokinin receptor (*CCKAR* gene 779T>C), and high-producer tumor necrosis factor genotype. Further studies are necessary to determine how genetic factors influence the clinical manifestations and therapeutical response in IBS patients.

Key words: Irritable bowel syndrome; Genetic factors; Gene polymorphisms; Twin studies; Familial aggregation

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INTRODUCTION

Irritable bowel syndrome (IBS) is defined according to Rome Ⅲ criteria as recurrent abdominal pain or discomfort for at least 3 d per month during the previous 3 mo associated with two or more of the following symptoms: improvement with defecation, onset associated with a change in the frequency of stools and/or onset associated with a change in form or appearance of stools[1,2]. There are four types of IBS: constipation-predominant IBS, diarrhea-predominant IBS, mixed IBS and unclassified IBS. Within one year, 75% of patients change subtypes. Population-based studies show prevalence of IBS to be 10%-20% and an incidence level of IBS at 1%-2% per year[3].

The precise etiology of IBS is still unknown, but there is evidence in the last decade regarding the contribution of genetic, infectious, psychosocial and dietary factors.

Although to date there has been little support found for the role of different genes in the development of IBS, growing evidence suggests that genetic factors may contribute to the etiology and clinical manifestations of IBS.

The evaluation of genetic influence is based on familial aggregation, twin studies, and genetic epidemiological studies focusing on gene polymorphisms.

FAMILIAL AGGREGATION

Although the family clustering of IBS has been noticed in medical practice for several years, Whorwell undertook

pioneering work regarding familial aggregation of IBS. He found that 33% of patients with IBS reported a family history of IBS compared with only 2% of the control group[4].

A family cluster study of 643 subjects from Olmsted County, USA, showed a significant association between having a first-degree relative with bowel problems and presenting with IBS [odds ratio, 2.3; 95% confidence interval (CI), 1.3-3.9]. Those who reported having a spouse with bowel problems were no more likely to present with IBS. The authors also concluded that familial associations may represent exposure to a similar environment as well as the influence of genetic factors[5].

A recent study that directly surveyed relatives showed a prevalence of IBS of 17% in patients' relatives *vs* 7% in spouses' relatives [odds ratio adjusted for age and sex 2.7 (95% CI, 1.2-6.3)]. When also adjusted for somatization score, the odds ratio was 2.5 (95% CI, 0.9-6.7). The authors concluded that IBS presents a familial aggregation due to genetic or intrafamilial environmental factors, but this may be partially explained by familial aggregation of somatization[6].

Some limitations of these studies were that only abdominal symptoms in first-degree relatives were assessed and that the IBS diagnosis was not confirmed by a specialist.

Some studies have shown that specific types of gastrointestinal illness behavior may be learned through modeling[7], thus biasing the data on genetic transmission.

A Japanese study showed that both patients with IBS and IBS nonconsulters were more likely than controls to present positive family history (33.9% *vs* 12.6%, $P < 0.001$, for patients; 26.1% *vs* 12.6%, $P < 0.01$, for nonconsulters). The parental history was associated with a significantly higher impact on clinical manifestations, including indigestion, diarrhea, constipation, anxiety. The authors concluded that a parental history of bowel problems represents a significant risk factor for development of IBS in Japan, as reported in USA. Patients with a family history present with more psychological distress than other patients[8].

TWINS STUDIES

The contribution of genetic factors to the development of IBS was assessed in several major twin studies.

The Australian study, conducted on 343 twin pairs, by Morris-Yates, in 1998, showed a higher concordance rate for IBS in monozygotic twins than in dizygotic twins (33.3% *vs* 13.3%). This study, revealing that 56.9% (95% CI, 40.6%-75.9%) of the variance is attributed to additive genetic factors, shows a substantial involvement of the genetic component in IBS[9].

The American study conducted by Levy and published in 2001, studied the concordance rate of IBS among 6060 twin pairs. The concordance rate in monozygotic twins was twice as high as that in dizygotic twins (17.2% *vs* 8.4%, $P = 0.03$). However, the number of dizygotic twins with IBS who have mothers with IBS was greater than the number of dizygotic twins with IBS who have co-twins with IBS (15.2% *vs* 6.7%, $P < 0.001$); data also showed that having a mother or a father with IBS are both independent predictors of irritable bowel status ($P < 0.001$) and both are stronger predictors than having a twin with IBS. Data about the other twin accounted for little additional predictive power. The study concluded that heredity contributes to development of IBS, but social learning has also an important influence[10].

In contrast with these studies, a British study published in 2005, which included 1870 twin pairs, showed an IBS prevalence of 17% in monozygotic twins and 16% in dizygotic twins. There was no significant difference regarding the concordance rates between monozygotic and dizygotic twins (28% *vs* 27%). Logistic regression analysis revealed that decreasing age and increasing psychosomatic score were independent factors associated with IBS. Somatization was shown to be moderately heritable. The study concluded that genetic factors are of little or no contribution to the development of IBS[11].

A Norwegian study published in 2006 showed a concordance for IBS significantly greater in monozygotic (22.4%) than in dizygotic (9.1%) twins ($P = 0.011$). The heritability of IBS was found to be 48.4% among females. Birth weight below 1500 g (adjusted odds ratio 2.4 (95% CI, 1.1-5.3)) influenced significantly the development of IBS, which occurred 7.7 years earlier in the low weight group than in higher weight groups[12].

Another recent twin study performed on 986 twin pairs and published in 2007 showed a polychoric correlation for monozygotic twins and IBS (0.47) larger than that for dizygotic twins (0.17). Genetic variance was 22%, but adjusting for anxiety and depression removed the statistical significance for IBS. The study concluded that genetic factors are involved in IBS, possibly mediated by the hereditability of anxiety and depression[13].

GENE POLYMORPHISMS

No single pathophysiologic mechanism explains entirely the clinical manifestations of IBS. Current evidence suggests that altered brain-gut axis is the key mechanism associated with disordered motility, visceral hypersensitivity and autonomic dysfunction[3,14]. Regulation of these connections occurs *via* numerous neurotransmitters such as CCK, VIP, substance P, serotonin (5-hydroxytryptamine, 5-HT). Recent studies have also shown the involvement of the corticotropin-releasing hormone (CRH) in stress-related pathophysiology of IBS and possibly in inflammation of the intestinal mucosa[15].

Genetic factors may influence all these mechanisms, affecting both central and peripheral levels of the brain-gut interrelations[16].

Some authors have shown that substances and genes involved in the brain-gut axis may represent the key factor solving IBS[14].

Gene polymorphisms involve the serotonergic, adrenergic and opioidergic systems, and genes encoding proteins with immunomodulatory and/or neuromodulatory features[17,18].

Serotonin polymorphisms

At the gastrointestinal level, 5-HT acts as a paracrine signalling molecule and as a transmitter released by serotonergic interneurons. Serotonin activates at least five types of receptors, influencing intestinal peristalsis, secretion and signalling in the brain-gut axis. Based on the differences in structure and function, seven types of 5-HT receptors have been described[18]. In patients with IBS, stimulation of 5-HT type 3 receptors may lead to cramps, urgency, diarrhea and colonic contractions. The serotonin removal from the sites of action is mediated by a specific protein, the serotonin reuptake transporter (SERT). Increased 5-HT release in the bowel may induce diarrhea, nausea, and vomiting[19].

A high level of 5-HT may result from exaggerated synthesis, excessive release, or inadequate uptake and inactivation. Modifications in the serotonin transporter, responsible for removing 5-HT from the interstitial space and terminating its action, may also contribute to gastrointestinal motility troubles[19].

Whereas no specific gene has been identified in association with IBS, recent studies have demonstrated the importance of polymorphisms in the promoter region of the serotonin reuptake transporter gene for motility disorders[19].

The *SERT* gene encoding the SERT protein is located on the chromosome 17q11.2-q1. A functional polymorphism, an insertion or deletion of 44 base pairs in the 5-HT-transporter-gene-linked polymorphic region (5-HTTLPR), was first reported in 1996 by Heils[20].

An association between 5-HTTLPR polymorphism and diarrhea in women with IBS has been reported[19]; however, insufficient numbers of constipation-predominant IBS patients represented a limitation of this study. Homozygous or heterozygous patients for the 5-HTTLPR deletion (the short allele) have decreased transcription of *SLC6A4*, reduced expression of the sodium-dependent serotonin transporter and, therefore, reduced reuptake of serotonin. Homozygous patients for the 5-HTTLPR insertion polymorphism (the long allele) present wth significantly slower colonic transit than heterozygous patients, whereas no difference regarding the colonic transit time is found between homozygous or heterozygous patients for the 5-HTTLPR deletion polymorphism[17,19].

The 5-HTTLPR polymorphism was also studied in various behavioral traits and psychiatric disorders; a recent study has shown that IBS patients homozygous for the short allele of 5-HTTLPR or carrying a STin2.9VNTR allele (polymorphism located in intron 2 of *SERT* gene) are significantly more likely to present a history of depression[20].

Another study has revealed that 5-HTTLPR long allele may be one pathway that activates negative emotion in females and has a contrary action in males[21].

A recent Chinese study has investigated the relationship between polymorphisms of the serotonin reuptake transporter and the IBS subtypes, and its influence on the efficacy of tegaserod treatment. This study suggests that individuals with the long allele genotype are vulnerable to develop IBS with constipation and respond poorly to tegaserod treatment[22]. Another study has shown that alosetron, a 5-HT type 3 receptor antagonist, relieves IBS-related pain and normalizes bowel function in women with diarrhea-predominant IBS. This study also suggests that this drug is more effective in homozygous patients than in heterozygous patients for 5-HTTLPR insertion. However, the small number of patients enrolled in this study does not permit a firm conclusion[23,24].

Interaction of serotonergic and adrenergic receptors

Adrenergic agents act upon the sensory and motor function of the human gastrointestinal tract, *via* α_2 adrenergic receptors (adrenoceptors). Three human α_2 adrenoceptors have been identified: the α_{2A}, α_{2B} and α_{2C} subtypes.

There is evidence that polymorphisms in the genes encoding these receptors may decrease the synaptic autoinhibitory feedback and increase presynaptic release of norepinephrine. Norepinephrine transporter modulates the synaptic level of norepinephrine. There is evidence of an interaction between serotonin and norepinephrine in the modulation of gastrointestinal function[25]. Associations have been observed between polymorphisms in *SLC6A4* or genes that encode α_{2A} and α_{2C} adrenoceptors and IBS phenotypes. A polymorphism in *ADRA2C*, the gene encoding the α_{2C} adrenoceptor, is associated with an increased likelihood of constipation in patients with gastrointestinal functional disorders ($P = 0.05$), and also with an increased likelihood of severe and frequent somatic symptoms. Polymorphisms in the genes encoding the α_{2A} adrenoceptor and the α_{2C} adrenoceptor are significantly associated with a high somatic symptom score[26].

In patients with functional dyspepsia, modified alpha-adrenoreceptor function and depression are common; features that are linked to a G-protein beta 3 (GNB3) subunit gene polymorphism (C825T), as shown in a study published in 2004. G-protein beta 3 subunit 825 *CC* genotype was significantly associated with unexplained (functional) dyspepsia; the odds ratio adjusted for age and sex for upper abdominal symptoms was 2.2 (95% CI, 1.4-3.3)[27].

Cholecystokinin

Cholecystokinin (CCK) is released by endocrine I cells within the duodenal and jejunal mucosa in response to the products of protein and fat digestion.

Patients with IBS have high fasting and postprandial plasma levels of CCK. The effects of CCK are mediated *via* CCK-A receptor and CCK-B receptor (also known as CCK1-R and CCK2-R) located in the peripheral and central nervous system. Therapeutical blockade of CCK-A receptors may stimulate gut motility and may

reduce colonic transit time in patients with constipation-predominant IBS[28].

A polymorphism in *CCKAR* gene (779T>C) in IBS patients with constipation is associated with slower gastric emptying. This suggests that, compared with the 779T variant, the 779C substitution results in an increased response to endogenous CCK, retarding the gastric emptying. Future confirmatory studies are needed, due to the small sample size in this study[29].

Cytokines

Although the definition of IBS states that no active inflammation causes symptoms, transient mucosal inflammation is considered to be an important factor for the manifestation of IBS.

Cytokines are involved in the regulation of the immune and inflammatory reaction with proinflammatory effects, such as tumor necrosis factor (TNF) and interferon, and with anti-inflammatory effects, such as interleukin 10 (IL-10) and transforming growth factor (TGF) β1.

A genetic predisposition to produce high or low amounts of a particular cytokine may modify the susceptibility to a certain disease, or affect its clinical manifestation. Some studies have shown no significant association between TGF β genotypes and IBS patients.

By contrast, a low prevalence of the high-producer genotype of IL-10 in patients with IBS has been noticed, suggesting the association between the predisposition to produce low amounts of this cytokine and IBS, or a possible protective role of high levels of IL-10. A genetic predisposition to produce low levels of anti-inflammatory cytokines may signify a compromised control of the inflammatory response[17,30].

Another study has shown that high-producer TNF-α genotype is more prevalent in IBS patients than in healthy subjects. Homozygous high-producer genotypes were rare in both groups; the heterozygous genotype was found in 41% of IBS patients *vs* only 26% of healthy controls. By contrast, no significant difference regarding the IL-10 genotypes prevalence was found in IBS patients and control group. The authors concluded that high producer TNF-α and low producer IL-10 genotypes were significantly more prevalent in IBS patients than control group (9% *vs* 3%, $P = 0.035$) and in diarrhea (20%) compared to other IBS subtypes (< 4%, $P = 0.026$)[30]. Another study showed a significantly low prevalence of the high-producer IL-10 genotype in IBS patients compared with controls (21% *vs* 32%)[31]. This difference might be related to variation in genotype frequencies according to ethnicity: the high-producer IL-10 genotype is significantly higher in the Irish population (34%) than in Africans (9.5%). A limitation of the study consisted of the assessment of only one anti-inflammatory cytokine polymorphism[17].

Post-infectious IBS

A recent study evaluated the involvement of genetic factors in post-infectious IBS; the authors capitalized on the opportunity to study these correlations after the contamination of the municipal water in a small rural town in Canada. They identified four candidates associated with post-infectious IBS: two located in Toll-like receptor 9 (the coding SNP rs352139 and the promoter SNP rs5743836), one involving the promoter SNP of E-cadherin (rs16260) and the other involving a promoter SNP of IL-6 (rs1800795). The authors concluded that after corrections for multiple comparisons, none of these associations is significant and stressed the importance of the further population studies for validations of the gene candidates in post-infectious IBS[32].

Psychological distress

Association between psychological distress and IBS may be due to common genetic factors, but this remains debatable.

The association between major depressive disorder and IBS (with a 13%-45% co-occurrence) may involve genetic and environmental common pathophysiological mechanisms[33]. A recent study has shown the lack of specificity regarding this association; chronic widespread pain related to fibromyalgia and chronic fatigue are also associated with IBS. The authors concluded that genetic and family environmental factors do not explain the association between IBS and major depressive disorder[33,34].

Another recent study has investigated the genetic compo-nent in the co-occurrence of IBS with psychological factors; the authors have shown that independent risk factors for IBS are: female gender, somatization, neuroticism, phobia; no environmental factors are significantly involved. Depression and neuroticism do not co-occur with IBS through common genetic factors, whereas somatization associated with IBS share common genetic components[35]. The authors concluded that identifying the genes involved in somatization may represent a key in understanding IBS etiology[35].

CONCLUSION

IBS is a multifactorial functional disorder, resulting from a complex interaction of genes, environment and psychosocial factors. Recent studies have shown that genes may play an important role in IBS. Thus, the environmental factors can trigger the clinical manifestations of IBS when acting on a certain genetic background.

Genetic factors may be directly linked to gastro-intestinal sensory and motor functions or cause initiation of the modifications underlying the symptoms in the presence of exogenous factors.

Further studies are necessary to develop the facts known so far about the genetic determination of the clinical features and therapeutical response in IBS.

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