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EDITORIAL

New Paradigm for Studying Genetic Contributions to Irritable Bowel Syndrome

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Irritable Bowel Syndrome (IBS) is common disabling condition that is associated with an estimated $8 billion per year in direct healthcare costs [1]. In the past few decades multiple studies have been published on the etiology of IBS, and several pathophysiological factors have been found to be significantly associated with IBS diagnosis, such as motility disturbances, visceral hypersensitivity, psychological distress, and immune dysregulation. However, none of these factors is sufficient by itself to explain the development of IBS. Therefore, it is widely believed that IBS is not caused by a single factor but rather the interaction of various biological, psychological, and social factors which interact to contribute to the etiology and maintenance of the disorder [2]. No single factor appears to be necessary for disease expression, and none may be sufficient in isolation from the others.

Considering this complex model of the causes of IBS, it is no surprise that genetic factors in IBS generally are not expected to follow a Mendelian inheritance pattern in which the disease is caused by a single gene [3–5]. Rather, it is thought that IBS is a complex genetic disorder with genes affecting the various etiological factors described above. It is, therefore, reasonable to expect that this complex model of IBS involving interactions between physiological vulnerabilities and psychosocial stressors will be matched at the molecular level by gene–gene and gene-environment interactions. The study by Saito et al. [6] in this issue of *Digestive Diseases and Sciences* is significant because it demonstrates that taking these interactions into account can unmask genetic contributions to IBS etiology where simple genetic association studies have failed to show an effect. This is the second study to show that a genetic polymorphism interacts with exposure to infectious gastroenteritis to contribute to the expression of post-infectious IBS; the first was the study by Villani et al. [7] which found that polymorphisms in Toll-like receptor 9, interleukin (IL)-6, and CDH1 were associated with an increased likelihood of the reporting of persistent gastrointestinal symptoms following exposure to a water-borne outbreak of gastroenteritis. These polymorphisms were not found to be associated with IBS developing in the absence of gastroenteritis [8]. These two studies likely herald a turning point in the evolution of studies on the genetic contributions to IBS and other complex diseases. This paradigm shift offers the promise of more precise estimates of disease prediction, provides greater insights into gene function, and, by suggesting how to ameliorate the impact of genetic risk, offers the potential of greater clinical impact.

The article by Saito and colleagues also points out the challenges in carrying out investigations of gene–environment interactions: such studies need to be hypothesis driven because the possible permutations of genetic polymorphisms and environmental exposures are nearly infinite. Several candidate gene studies have been associated with IBS [3–5]. These include, among others, serotonin receptor and transporter genes [9–17], adrenoreceptor genes [18–22], and genes in the inflammatory pathway [7, 8, 23–25]. In addition, multiple environmental factors have been shown to play a role in IBS, such as an affluent childhood, early infant trauma (e.g., gastric suction at birth, low birth weight, and severe nutritional deficits), sexual or physical abuse history, life stress, military deployment,

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social learning, and gastroenteritis [26–31]. Gene studies should carefully explore the interactions of these environmental effects and polymorphisms in IBS. In identifying an a priori hypothesis, a clear rationale is needed that links the gene's presumed function to one of the endophenotypes believed to explain the symptoms of IBS (e.g., pain hypersensitivity, stress reactivity, immune dysregulation), and an environmental exposure that is already known to be associated with this endophenotype. In the Saito study, the authors focused on a possible association between 5HTTLPR and a history of abuse based on previous evidence that this polymorphism is linked to the development of psychiatric disorders in the presence of an abuse history [32], but they did not find support for this gene–environment interaction in IBS. They based their second hypothesis of an interaction between the GNbeta3 polymorphism and a history of gastroenteritis on previous evidence that GNbeta3 is involved in immune regulation, and their hypothesis was supported. However, there are other genetic markers more closely associated with impaired immune function in IBS, such as IL-10 [23], which might have been more logical than GNbeta3 to test for their interaction with prior gastroenteritis. The authors do not explain their preference for GNbeta3 over these other genes.

Other well-known limitations to IBS genetic association studies also apply to studies of gene–environment interactions: (1) the IBS phenotype is imprecise because it is based on symptoms ascertained by self-report and a negative medical work-up, which may lead to heterogeneity in the samples studied; (2) validated, objective measures of environmental exposures and prospective research designs are preferable to chart reviews and retrospective self-report to protect against measurement error. With these limitations in mind, replication of findings by independent investigators will continue to be necessary to move this field forward.

Thus, for IBS, multiple genes likely contribute in an additive or synergistic fashion and critical environmental exposures interact with these genetic risk factors to trigger expression of the disease phenotype only if the environmental exposure is present. To date, up to 60 candidate genes have been identified in IBS [33], although few have been independently replicated. Researchers are therefore at an exciting crossroads where the use of complex models that include genes, endophenotypes, and environmental factors may start facilitating the elucidation of important pathways for this enigmatic disorder. For example, the 5HTTLPR (gene) has been associated with higher rectal pain ratings [34], anxiety, and depression [35] in IBS patients (endophenotype), and interacts with stressful life events in the expression of major depression (a possible environmental factor) [36]. Studies combing these factors into one model are greatly needed to unravel the mystery of IBS etiology and develop more personalized treatment models.

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