Annals of Gastroenterology (2013) **26,** 87-88

Identifying and testing candidate genetic polymorphisms in irritable bowel syndrome: association with TNFSF15 and tumor necrosis factor-α

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Title: Identifying and testing candidate genetic polymorphisms in the irritable bowel syndrome (IBS): association with TNFSF15 and TNFα

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Journal: *Gut* 2012, in press

Summary

Although irritable bowel syndrome (IBS) is extremely common, few studies have examined the interaction between environmental factors and genetic polymorphisms in IBS. Over the last decade, increasing evidence suggests that genetic factors contribute to the development of IBS. In a recent study published in *Gut*, Swan *et al* identified genetic polymorphisms, which may be associated with IBS [1]. Swan hypothesized that genetic markers whose expression was altered by *Campylobacter jejuni* (*C. jejuni*) gastroenteritis may be linked to IBS with diarrhea (IBS-D), which closely resembles post-infectious IBS (PI-IBS) [1]. Swan's hypothesis was that patients with IBS-D have a genetic tendency to overreact to inflammatory insults and show immune activation. In a two-part study, healthy patients, patients 6 months after *C. jejuni* infection, and patients with IBS-D and IBS with constipation (IBS-C) underwent rectal biopsies for gene expression analysis and peripheral blood cell cytokine (inflammatory marker) assessment. Polymorphisms in gene expression that were altered by *C. jejuni* gastroenteritis were similar to mucosal gene expression seen in IBS-D. Part one of the study assessed gene expression in the rectal mucosa both 6 months after *C. jejuni* infection and in chronic IBS patients compared with healthy volunteers. The authors showed that mucosal expression of seven genes was altered in IBS, and that these alterations in mucosal expression were similar to those seen in PI-IBS after *C. jejuni* infection. Part two of the study assessed 21 known single-nucleotide genetic polymorphisms (SNPs) in the seven genes identified in part one, and one SNP in both the tumor necrosis factor-α [2] and interleukin-10 genes, previously linked to IBS [3]. The authors showed that the polymorphism in the *TNSFSF15* gene, previously linked to Crohn's disease, was associated with IBS-D. The authors suggested that there is a common underlying pathogenesis between IBS-D, PI-IBS and Crohn's disease. Based on these findings, Swan *et al* concluded that there is a genetic tendency for a pro-inflammatory state in IBS and investigators must search for biomarkers that cause inflammation, and that anti-inflammatory agents can be used to treat IBS [1].

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Conflict of Interest: None

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Received 8 November 2012; accepted 8 November 2012

Opinion

In evaluating the contribution of genetics in IBS one must examine the specific contribution of PI-IBS and the role that pro-inflammatory cytokines play in development of IBS. Over the last decade, epidemiological studies of familial aggregation as proven by various monozygotic and dizygotic twin studies [4] suggest a genetic contribution to IBS and indicate that there is a clustering of IBS in families [5,6]. In particular, it is believed that genetic variations in the immunological components of the body, specifically susceptibility genes involved in the maintenance of the epithelial barrier, innate immunity and the interactions with bacteria in the gut are associated with IBS. It has been hypothesized that cytokine gene polymorphisms are a potential mechanism of IBS in patients without previous gastrointestinal infection and that residual or reactivated inflammation at the molecular level is the underlying pathogenesis of PI-IBS.

Post-inflammatory changes in the gut produce chronic alteration of the immune system at that molecular level which may target the enteric nervous system and smooth muscle fibers and affect the secretory function of the gut mucosa. It is believed that infectious episodes lead to histological

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alteration of the mucosa and present as IBS. Mutations in cytokine-producing genes may also make some individuals more susceptible to infectious gastroenteritis, which could cause PI-IBS or lead to the development of primary IBS [7,8].

In this elegant study, Swan *et al* examined 7 important genetic polymorphisms associated with IBS. The authors in this study identified genes abnormally expressed in the rectal mucosa of patients recovering from *Campylobacter* enteritis (the PI-IBS) and examined the up-regulation of inflammatory cytokines that are produced by immune cells. By identifying certain genes, Swan *et al* effectively narrowed the number of inflammatory susceptibility loci that deserve to be included in future studies. This study fits into a growing literature linking inflammatory markers to IBS.

Although this study helps us understand the genetic of IBS, it only examines a few polymorphisms associated with IBS, and it does not confirm several genes and pathways associated with IBS in previous studies [9-11]. IBS is a multifactorial disorder that cannot be explained by genetics alone. Environmental contributions-such as diet, smoking, early exposure to infectious organisms and colonic micro flora play a significant role in the disease process.

A relative strength of this study is that it is larger than many other studies testing candidate genetic polymorphisms. However, this study still has a small sample size, and therefore has the tendency to have false positive findings. Anytime genetic polymorphism are identified and tested as they are in this study, because of the large number of genes (20,000) and millions of gene variants, investigators will observe positive associations between hypothesized polymorphisms and complex functional gastrointestinal disorders by chance. However, until the gene polymorphisms in this study are replicated in separate and appropriately powered cohorts, the genetic tendency of a pro-inflammatory state of IBS cannot be confirmed.

Also, it is important to note that the clinical phenotype of IBS is not stable [6,12], making a genotype phenotype association extremely difficult to prove. In addition, this study uses a conventional dichotomous (affected or unaffected) approach, with no accommodation for the intermediate state, common in IBS.

Furthermore, the results of this study are different from conclusions in other studies. The TNFSF15 genetic marker in this study is only correlated with IBS-D, which differs from a recent study that correlates it with IBS-D and IBS-C [13]. Intestinal permeability was only increased in patients with PI-IBS, which differs from prior results published by the same and other groups [14].

Although this study is an important step in identifying susceptibility loci for IBS, and understanding the interplay between environmental factors and genetic polymorphisms in IBS, we are still far from having a mechanistic understanding of this complex genetic disorder. IBS is a heterogeneous, unstable disorder, without a well-defined molecular pathway or established biomarkers whose development is clearly multifactorial. The appropriate identification of susceptibility loci for IBS will likely require a genome-wide approach [15], testing thousands if not millions of SNPs whereby multiple testing issues apply. Nonetheless, studies such as this one are incredibly important because, by better understanding the genetics of IBS, we can hope to better determine the response to therapy.

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