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Genetics of Irritable Bowel Syndrome

Yuri A. Saito, M.D., M.P.H. and Nicholas J. Talley, M.D., Ph.D.

Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, Minnesota, and Jacksonville, Florida

Abstract

Irritable bowel syndrome (IBS) is one of the most common diagnoses made by gastroenterologists and primary care providers alike, and yet the underlying mechanism remains poorly understood. Family and twin studies suggest that IBS may have a genetic basis. Several candidate gene association studies have been performed, but thus far, they have failed to clearly identify an “IBS gene.” Epidemiological studies are needed to facilitate phenotype definition and identify relevant environment risk factors that will need to factor in gene and environment interactions in all future genetic studies. As genetic research in IBS is relatively nascent, much opportunity, as well as many challenges, exists in identifying the genes responsible for IBS.

WHY DO WE THINK THERE COULD BE A GENE FOR IBS?

Great strides have been made in our understanding of the human genome. In the wake of the Human Genome Project, which ambitiously sequenced the entire human genome, it is increasingly clear that genes play an important role in human health and disease. What is also apparent in this “post-genome” era is that there are many pieces of the genetic puzzle, but exactly how the puzzle pieces result in normal or abnormal body function remains a mystery for most diseases. With knowledge of the DNA sequence in hand, geneticists, genetic epidemiologists, statistical geneticists, and clinical researchers are attempting to identify the gene or set of genes causing many of today’s common diseases, such as heart disease and cancer. The discovery of the *NOD2/CARD15* (nucleotide-binding oligomerization domain protein 2/caspase recruitment domain-containing protein 15) gene as a major locus for Crohn’s disease represents a major scientific advance in the field of gastrointestinal (GI) research (1, 2).

The idea of a gene causing irritable bowel syndrome (IBS) is appealing. Although diet and stress have been clearly linked to IBS, the identification of risk factors such as these has not resulted in better diagnostic tests or pharmacological therapies that patients and their health-care providers are seeking. An insight into the underlying molecular mechanisms for the disease may facilitate test and drug development. Genetics provides this potential promise if disease-causing genes—referred to as disease-susceptibility loci—for IBS are discovered.

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Reprint requests and correspondence: Yuri A. Saito, M.D., M.P.H., Miles and Shirley Fiterman Center for Digestive Disease, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905.

CONFLICT OF INTEREST

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Besides the disease etiology, the other hope that understanding the genetics of IBS offers is that of the identification of genes that determine the response to therapy.

Traditional genetic diseases were rare diseases caused by a single or few major mutations in a single gene that were transmitted through families in a predictable (*i.e.*, autosomal dominant or autosomal recessive) manner. On the other hand, IBS is not a rare, lethal disease, and thus, is unlikely to be a classic Mendelian disease that is caused by one gene. Rather, if there is indeed a genetic basis for IBS, IBS is likely a “complex genetic disease,” caused by multiple genes that interact with environmental risk factors to result in IBS symptoms. Furthermore, the genetic variants responsible for IBS may be commonly present in the general population, and each genetic variant may have a “weak” effect, resulting in IBS symptoms that may not be easy to discover. As illustrated in Figure 1, the variability in the clinical presentation of IBS may, in part, be explained by an underlying genetic and environmental heterogeneity. Nonetheless, this paradigm, at present, is speculative, and additional studies are needed to successfully identify the genes for IBS, if they indeed exist.

WHAT EVIDENCE IS THERE FOR AN IBS GENE?

Current evidence for an IBS gene is admittedly limited at present. Importantly, several studies suggest that IBS and other gastrointestinal symptoms do run in families—a critical feature of genetic diseases. When asked if they have a family member with IBS, approximately 33% of outpatients with IBS will report a positive family history of IBS, compared with 2% of outpatient controls (3). Furthermore, when specific relationships have been evaluated, 26–34% of patients will have a parent with IBS, compared with 13% of control patients (4). Furthermore, children of parents with IBS are also twice as likely to see a provider for abdominal complaints as children of parents without IBS (5). Young adults who as children had recurrent abdominal pain were nearly three times as likely to have persistent IBS-like symptoms at 5–13 yr of follow-up if there was a concurrent sibling with abdominal pain (6). However, a major limitation of the majority of these studies is that the IBS status of the relatives were collected from the patient, but not collected or verified in the relative. In another study where family members were directly queried regarding bowel symptoms, between 54 and 68% of patients with IBS had an affected first-degree family member, compared with 19–36% of controls without IBS (7). Overall, it was estimated that between 15 and 37% of case-relatives are affected with IBS, compared with 4–16% of control-relatives, depending on whether the source of the information was the proband (the case or control), the participating relatives, or a combination of both sources, whereby the proband data about relatives were used when data from a specific relative were not available.

Twin studies represent a specific type of family study that provides a unique opportunity to discern the genetic and environmental contributors to disease. Because monozygotic twins share the exact same genetic code and dizygotic twins share half of the same genetic code, comparing concordance rates between monozygotic and dizygotic twins allows the opportunity to quantitate the contributions that genetics and environment each make to the development of the disease. Five twin studies demonstrate that the genetic contribution to IBS appears to range between 0 and 20% (8–12). The reasons for the heterogeneity in genetic liability estimates are not clear; they may represent true population-based differences, but are likely the result of methodological differences with respect to how IBS status was defined and how the information was collected.

Four of these twin studies performed additional modeling of the correlations between members of a twin pair to resolve whether the phenotypic variance observed could be attributed to the genetic or environmental components. Testing a series of models, all but the

British Twin Study found that the best-fit models included components for an additive genetic component and individual environmental exposures. The genetic heritability was estimated to be 22%, 48%, and 57% in the Minnesota, Norwegian, and Australian twin studies, respectively, whereas the individual environmental contributors ranged from 43 to 78%. Importantly, shared environment did not appear to be an important predictor of phenotypic variance in these three studies. Furthermore, none found that the genetic effect was due to a dominant genetic effect. Thus, based on the results of the twin studies, it appears that IBS is caused by both genetics and unique environment. Although the results of these twin studies are revealing, they cannot conclusively prove that IBS did not aggregate between twins due to a specific shared household risk factor (*e.g.*, diet, lifestyle, abuse, or infection) or due to shared genes for another non-GI entity such as somatization, psychiatric disease, or susceptibility to infection. Furthermore, social learning and other aspects of a shared childhood family environment exist as confounders in twin and family studies, and because they are difficult to assess and quantitate, have likely not been adequately controlled for by statistical modeling. The Virginia Twin Study also showed that the proportion of dizygotic twins with IBS who had an affected mother was greater than the proportion of dizygotic twins with IBS with an affected co-twin, and that having a mother or father with IBS was an independent predictor of IBS (8). In summary, these studies suggest that both heredity and parental influences may be important in the development of IBS.

WHAT GENES HAVE BEEN EVALUATED IN IBS?

Several investigators have evaluated specific “candidate” genes (Table 1). Candidate genes are genes that are *a priori* nominated by investigators based on the biological plausibility that the gene’s protein product could play a role in disease pathophysiology. Polymorphisms are the common genetic variations within these genes postulated to be responsible for disease development. The gene that has received the most attention from multiple investigators is the serotonin transporter gene (*SLC6A4*, solute carrier family 6, member 4) (Fig. 2). The serotonin transporter is the protein located on the presynaptic terminal that is responsible for the re-uptake of serotonin from the synaptic cleft. Mice lacking this gene, and therefore not expressing the transporter, exhibited an altered colonic motility (13). The genetic polymorphism most extensively studied—called the 5-HTTLPR for serotonin transporter-linked polymorphic region—is in the promoter region of this gene. The studies evaluated this polymorphism in U.S., Turkish, and Korean patients; however, they did not find this polymorphism to be more common in cases than controls (14–17). A recent meta-analysis has also concluded that this polymorphism is neither associated with IBS, nor associated with its subtypes (18). On the other hand, two studies have found that this polymorphism may predict response to therapy. Specifically, the LL genotype has been associated with a better treatment response to alosetron, a 5-HT₃ (5-hydroxytryptamine receptor 3) receptor antagonist (19), and that the S allele was associated with predicting the response to tegaserod therapy among individuals with constipation-predominant IBS in an allele dose-dependent manner (20).

Besides the serotonin transporter gene, other studies have evaluated the 5-HT_{2A} receptor gene (*5-HT2A*, 5-hydroxytryptamine receptor 2A) (21), the norepinephrine transporter gene (*NET*) (14), the alpha_{2A}-adrenergic receptor gene (*ADRA2A*) (14), alpha_{2C}-adrenergic receptor gene (*ADRA2C*) (14), as well as inflammatory genes including interleukin-10 (*IL-10*) (22, 23), transforming growth factor- β 1 (*TGF- β*) (22), tumor necrosis factor-alpha (*TNF- α*) (23), and the β 3 subunit G protein (*GN β 3*) (24, 25). Positive associations were observed between the AA or GA genotype of the –1082G/A polymorphism on the *IL-10* gene and IBS, as well as the heterozygote GA genotype on the –308G/A polymorphism on the *TNF- α* gene. More recently, a functional mutation has been discovered in a patient with IBS in the *SCN5A* (sodium channel, voltage-gated, type V,

alpha subunit) gene encoding a sodium channel found in the intestine (26, 27). One study of the polymorphism in the fatty acid amide hydrolase gene (*FAAH*), whose enzyme inactivates endocannabinoids, has shown an association between the 385C>T polymorphism with diarrhea-predominant and mixed IBS (28). However, further reproduction of these positive studies in other patient samples and mechanistic studies confirming the role of these polymorphisms in causing IBS have yet to be published and are absolutely required before firm conclusions can be drawn as to whether they lie in the IBS causative pathway. Spurious associations between polymorphisms and disease are the rule rather than the exception, as reported by a recent review of candidate gene association studies, which are the result of a lack of adjustment for multiple testing or inappropriate selection of controls who are not matched to cases based on features such as gender, setting (*i.e.*, patients vs nonpatients), or race (29).

WHAT IN THE CURRENT STATE OF KNOWLEDGE IS LACKING?

In the absence of an identified gene for IBS, at present, the major obstacle to gene discovery in IBS is the lack of additional clinical and epidemiological information regarding IBS. Prior to concluding that IBS is a complex genetic disease, it would be helpful to test in a rigorous manner whether IBS is truly not a Mendelian disorder. Furthermore, it would be helpful to clearly identify the environmental risk factors that will need to be adjusted for in any genetic studies of IBS. Although the twin studies argue that familial clustering of IBS is not due to shared environment, further study of household effects such as shared lifestyle (*e.g.*, diet and exercise), learned illness behavior, and shared risk factors (*e.g.*, abuse or infection) is critical. Certainly, it is also possible that IBS is also the result of genes that not only determine bowel symptoms, but those that determine personality and psychological comorbidity. Well-defined phenotypes are also critically important, as combining individuals with clinical and etiological heterogeneity will decrease an investigator's ability to detect modest allele and genotypic frequency differences. More accurate and objective disease definitions of IBS—including subtypes—will be crucial for future genetic studies in IBS.

WHERE DO WE GO FROM HERE?

Various approaches exist for new gene discovery. Some approaches require collection of families (*e.g.*, linkage studies), but nonfamily-based approaches (*e.g.*, association studies) exist as well. The method selected by researchers will depend on individual hypotheses as well as the available resources as no single approach is the "best." Sample sizes needed for the studies will depend on the approach, number of genetic markers studied (as adjustment for multiple testing will be required), and the minor allele frequencies of the genetic markers. For example, by study design, the numbers vary considerably: linkage studies may require 50–500 families (entire nuclear families, multigenerational families, or relative-pairs), candidate gene studies may require 100–1,000 cases and controls, and genome-wide association studies may require 5,000–10,000 subjects. Because of the large sample sizes needed, a collaboration between multiple centers may be required in order to recruit the numbers needed to adequately power such studies. A careful characterization of each study subject—such as predominant symptom, racial information, exposure to relevant risk factors, psychological comorbidity, and social environment—will be necessary as well to allow for gene and environment interactions.

Although the search for a disease gene is challenging, it is important to keep in mind that discovery of even a single gene for IBS would provide great insight into the pathophysiology of the condition and lead to studies of new molecular targets that could hopefully lead to better, objective diagnostic testing and treatments for IBS.

References

1. Ogura Y, Bonen DK, Inohara N, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature*. 2001; 411:603–6. [PubMed: 11385577]
2. Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature*. 2001; 411:599–603.
3. Whorwell PJ, McCallum M, Creed FH, et al. Non-colonic features of irritable bowel syndrome. *Gut*. 1986; 27:37–40.
4. Kanazawa M, Endo Y, Whitehead WE, et al. Patients and nonconsulters with irritable bowel syndrome reporting a parental history of bowel problems have more impaired psychological distress. *Dig Dis Sci*. 2004; 49:1046–53. [PubMed: 15309899]
5. Levy RL, Whitehead WE, Von Korff MR, et al. Intergenerational transmission of gastrointestinal illness behavior. *Am J Gastroenterol*. 2000; 95:451–6.
6. Pace F, Zuin G, Di Giacomo S, et al. Family history of irritable bowel syndrome is the major determinant of persistent abdominal complaints in young adults with a history of pediatric recurrent abdominal pain. *World J Gastroenterol*. 2006; 12:3874–7. [PubMed: 16804973]
7. Saito YA, Zimmerman JM, Harmsen WS, et al. Irritable bowel syndrome aggregates strongly in families: A family-based case-control study. *Neurogastroenterol Motil*. 2008; 7:790–7.
8. Levy RL, Jones KR, Whitehead WE, et al. Irritable bowel syndrome in twins: Heredity and social learning both contribute to etiology. *Gastroenterology*. 2001; 121:799–804. [PubMed: 11606493]
9. Morris-Yates A, Talley NJ, Boyce PM, et al. Evidence of a genetic contribution to functional bowel disorder. *Am J Gastroenterol*. 1998; 93:1311–7.
10. Mohammed I, Cherkas LF, Riley SA, et al. Genetic influences in irritable bowel syndrome: a twin study. *Am J Gastroenterol*. 2005; 100:1340–4. [PubMed: 15929767]
11. Bengtson MB, Ronning T, Vatn MH, et al. Irritable bowel syndrome in twins: Genes and environment. *Gut*. 2006; 55:1754–9.
12. Lembo A, Zaman M, Jones M, et al. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: A twin study. *Aliment Pharmacol Ther*. 2007; 25:1343–50.
13. Chen JJ, Li Z, Pan H, et al. Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: Abnormal intestinal motility and the expression of cation transporters. *J Neurosci*. 2001; 21:6348–61. [PubMed: 11487658]
14. Kim HJ, Camilleri M, Carlson PJ, et al. Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. *Gut*. 2004; 53:829–37. [PubMed: 15138209]
15. Pata C, Erdal ME, Derici E, et al. Serotonin transporter gene polymorphism in irritable bowel syndrome. *Am J Gastroenterol*. 2002; 97:1780–4.
16. Yeo A, Boyd P, Lumsden S, et al. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut*. 2004; 53:1452–8.
17. Lee DY, Park H, Kim WH, et al. Serotonin transporter gene polymorphism in healthy adults and patients with irritable bowel syndrome. *Korean J Gastroenterol*. 2004; 43:18–22.
18. Van Kerkhoven LA, Laheij RJ, Jansen JB. Meta-analysis: A functional polymorphism in the gene encoding for activity of the serotonin transporter protein is not associated with the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007; 26:979–86.
19. Camilleri M, Atanasova E, Carlson PJ, et al. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2002; 123:425–32.
20. Li Y, Nie Y, Xie J, et al. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci*. 2007; 52:2942–9.
21. Pata C, Erdal E, Yazc K, et al. Association of the –1438 G/A and 102 T/C polymorphism of the 5-*Ht2A* receptor gene with irritable bowel syndrome 5-*Ht2A* gene polymorphism in irritable bowel syndrome. *J Clin Gastroenterol*. 2004; 38:561–6.

22. Gonsalkorale WM, Perrey C, Pravica V, et al. Interleukin 10 genotypes in irritable bowel syndrome: Evidence for an inflammatory component? *Gut*. 2003; 52:91–3. [PubMed: 12477767]
23. Van Der Veek PP, Van Den Berg M, de Kroon YE, et al. Role of tumor necrosis factor-alpha and interleukin-10 gene polymorphisms in irritable bowel syndrome. *Am J Gastroenterol*. 2005; 100:2510–6.
24. Saito YA, Locke GR 3rd, Zimmerman JM, et al. A genetic association study of 5-HTT LPR and GNBeta3 C825 T polymorphisms with irritable bowel syndrome. *Neurogastroenterol Motil*. 2007; 19:465–70. [PubMed: 17564628]
25. Andresen V, Camilleri M, Kim HJ, et al. Is there an association between GNBeta3-C825 T genotype and lower functional gastrointestinal disorders? *Gastroenterology*. 2006; 130:1985–94. [PubMed: 16762621]
26. Locke GR 3rd, Tester DJ, Saito YA, et al. Sodium channel mutations and polymorphisms in people with IBS— potential role for an ion channelopathy. *Gastroenterology*. 2006; 130(Suppl 2):A739.
27. Strege PR, Saito-Loftus YA, Tester DJ, et al. G298 S mutation in Nav1. 5 in a patient with irritable bowel syndrome reduces sodium current density and mechanosensitivity. *Gastroenterology*. 2007; 132(Suppl 2):A148.
28. Camilleri M, Carlson P, McKinzie S, et al. Genetic variation in endocannabinoid metabolism, gastrointestinal motility, and sensation. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294:G13–9. [PubMed: 17962356]
29. Hirschhorn JN, Lohmueller K, Byrne E, et al. A comprehensive review of genetic association studies. *Genet Med*. 2002; 4:45–61.

Figure 1.

IBS may be a complex genetic disease caused by multiple genes (represented by genes A–F) with one or multiple genetic variations (arrows) of modest effect responsible for IBS symptoms. The clinical heterogeneity of IBS may perhaps be explained by the underlying genetic heterogeneity.

Figure 2.

The serotonin transporter gene (*SLC6A4*) contains the 5-HTT LPR polymorphism that results in a 44 bp insertion or deletion of repeat elements 6–8 in the promoter region. This polymorphism results in a long and a short transcript with functional differences.

Table 1**Candidate Genes**

Receptors:Alpha-2A-adrenergic receptors (*ADRA2A*)Alpha-2C-adrenergic receptors (*ADRA2C*)5-HT_{2A} receptor (*5-HT2A*)**Neurotransmitter transporters:**Serotonin transporter (*SLC6A4*)Norepinephrine transporter (*NET*)**Neurotransmitter metabolism:**Fatty acid amide hydrolase (*FAAH*)**Inflammatory markers:**Interleukin-10 (*IL-10*)Transforming growth factor- β 1 (*TGF- β 1*)Tumor necrosis factor-alpha (*TNF- α*)**Intracellular cell signaling:**G protein β 3 subunit (*GN β 3*)**Ion channels:**Sodium channel (*SCN5A*)