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The Role of Genetics in IBS

Yuri A. Saito, MD, MPH[Assistant Professor of Medicine]

Division of Gastroenterology and Hepatology Mayo Clinic, Rochester, MN

Abstract

IBS is a common disorder that has been shown to aggregate in families, to affect multiple generations, but not in a manner consistent with a major Mendelian effect. Relatives of an individual with IBS are two to three times as likely to have IBS, with both genders being affected. The estimated genetic liability ranges between 1–20%, with heritability estimates ranging between 0–57%. Although the role of childhood events such as nasogastric tube placement, poor nutrition, abuse, and other stressors have been clearly associated with IBS, these factors have not been studied in families and are unlikely to completely explain the clustering of bowel dysfunction observed in family studies. Furthermore, the familial clustering of IBS does not appear to be explained by psychological traits, based on family studies as well as candidate gene studies of functional variants associated with other psychiatric disorders. To date, over a hundred genetic variants in over 60 genes from various pathways have been studied in a number of candidate gene studies with several positive associations reported. These findings suggest that there may be distinct, as well as shared, molecular underpinnings for IBS and its subtypes. Much new and confirmatory work remains to be performed to elucidate the role of specific genetic variants in IBS development, as well as the specific ways the genes and environment interact to result in IBS susceptibility.

Keywords

Irritable bowel syndrome; IBS; genetics; gene; complex genetic disease

Introduction

As discussed in previous chapters, Irritable Bowel Syndrome (IBS) is a chronic disorder characterized by abdominal pain or discomfort and diarrhea and/or constipation that can be associated with altered gastrointestinal motility and visceral sensation. The chronicity of IBS symptoms and the lack of a cure or effective treatments result in loss of work and school productivity and impaired personal and health-related quality of life.¹ Patients, their relatives, and friends frequently ask difficult questions, such as why *they* developed IBS. Although diet, psychological factors, infection, and gut flora may attenuate IBS symptoms, there is no simple answer to this question. As other family members may concurrently have bowel disturbances, the role of genes in disease development—and the sense of personal

Corresponding author for proof and reprints: Yuri A. Saito Loftus, MD, MPH, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, Phone: (507) 538-7637, Fax: (507) 538-5820, saito.yuri@mayo.edu.

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destiny it invokes--is somewhat intuitive, easy to accept, but also difficult to refute with facts or objective findings arguing the contrary.

Great advances have been made in the field of genetics in recent years. As the efficiency, ease, and cost of genotyping has decreased, our understanding of DNA sequence, structure, and function has improved dramatically. Previously, laboratory-based study of the human genome was often restricted to known genes and coding exon regions and study of a handful of genetic variants. Now, high-throughput technology allows genotyping of thousands to a million genetic markers across the genome and sequencing of nearly the entire [coding] human genome is now possible. Furthermore, advances in data storage and analysis of these large quantities of data has led to the discovery of susceptibility loci for a number of diseases including, notably, Crohn's disease. These amazing scientific strides have led many to believe that "Virtually every human ailment, except perhaps trauma, has some basis in our genes." (www.genome.gov). This premise has appealed to many IBS researchers and several have commenced in trying to identify an IBS gene, or set of genes.

Despite the acceptance by some that genes may cause—or at least contribute to the development of—IBS, careful examination of the body of literature is necessary to determine whether there is sound basis for this theory as gene discovery still requires considerable time, effort, and thus, financial resources. Certainly, alternative hypotheses—such as environmental exposures—exist and can not be ignored as important players in IBS. This article will provide a summary of the studies around the competing hypotheses of "gene v. environment" or "nature v. nurture" in IBS. An overview of family studies, candidate gene studies, and alternative hypotheses for IBS will be covered to provide the reader an overview of the works conducted in this area.

IBS as a complex genetic disorder

Classic Mendelian genetics diseases are typically caused by a few highly penetrant genetic defects on a single gene and are transmitted in a typical pattern through families. Mendelian diseases follow an autosomal dominant, recessive, co-dominant, or X-linked pattern of transmission through pedigrees. Recent genetic studies have focused less on Mendelian disorders but on complex genetic diseases. A "complex genetic disease" is defined as a multifactorial genetic disorder resulting from multiple genetic variants on several genes (i.e. polygenic) with contributions from environment and lifestyle. These genetic effects are modest in that the presence of a specific variant is rarely sufficient on its own to result in disease development. Complex genetic diseases are still heritable in that they tend to aggregate in families, but not in the same predictable fashion as classic Mendelian disorders.

Many common diseases of significant public health interest are thought to be complex disorders. Heart disease, hypertension, diabetes, obesity, autism, and mood disorders are a few of the diseases and disorders under study by geneticists and genetic epidemiologists. In gastroenterology, Crohn's disease is the best example of a complex genetic disorder with successful susceptibility loci identification. Through a combination of family-based linkage studies, candidate gene and fine-mapping studies, as well as genome-wide association studies have led to the identification of several genes—such as *NOD2*, *ATG16L1*, *IL23*, *IL12B*, *STAT3*, *NKX2-3*—found to be consistently associated with Crohn's disease.² These discoveries offer the promise that if gene discovery was possible in this complex gastrointestinal disorder, that successful gene discovery is feasible in other multifactorial disorders and diseases including IBS.

Despite the discovery of several genetic loci involved in Crohn's disease development, it is clear that genes alone do not cause the disease and that environmental contributions—such as diet, smoking, early exposure to infectious organisms, and colonic microflora—are still

important. A similar gene-environment paradigm could be proposed for IBS (Figure 1) where a combination of genetic factors and environmental factors result in the alterations in gastrointestinal sensation and motor function that ultimately result in symptom manifestation. Genetic variation in genes that encode proteins that regulate gender-based biological processes, control or modulate central or peripheral sensation and motility, or even regulate brain response to stress would be the obvious first candidates for IBS. These factors, interacting with environmental factors such as diet, infection, early life trauma and stress, are likely responsible for the overall IBS phenotype. However, the specific combinations of genetic variants and environmental factors likely can in part explain the clinical heterogeneity of IBS. Hence, it is conceivable and likely that there are different genes responsible for diarrhea than those responsible for constipation, and other genetic variants that predispose an individual to developing or sensing abdominal pain required for IBS that is not generally present in the non-painful functional disorders such as functional constipation and functional diarrhea. Exploring gene-environment interactions will be important if one postulates that IBS is a multifactorial, polygenic complex genetic disorder.

IBS and heritability

Genetic diseases—complex or Mendelian—must run in families. Several studies of patients with IBS suggest that this disorder aggregates in families, and thus, appears potentially heritable. Children with persistent recurrent abdominal pain who were found to report IBS-like symptoms as adults were almost three-fold as likely to have at least one sibling with similar symptoms when compared to children-now-adults without IBS-like symptoms (40% v. 6%, $p<0.05$).³ Another study of IBS outpatients showed that one-third reported another family member with IBS, even in patients without a concurrent psychiatric diagnosis.⁴ In another study, having a first-degree relative with IBS was one of the characteristics found to be predictive of IBS over other gastrointestinal disorders among outpatients consulting their general practitioner for chronic abdominal pain.⁵

The majority of original studies evaluating familial clustering of IBS has been based predominantly on patient report of having another affected family member with IBS—proxy reporting. However, one study by our group has shown that accuracy of patient reporting on a specific relative's IBS status is poor.⁶ As a consequence, a large family case-control study was performed which collected bowel symptom and medical history data directly from cases, controls, and their first-degree relatives. This study of 477 cases, 1492 case-relatives, 297 controls, and 936 control-relatives found that 50% of case- and 27% of control-families had at least one other relative with IBS ($p<0.05$) (Figure 2).⁷ The magnitude of this effect was an odds ratio of 2.75 (95%CI: 2.01–3.76). When looking at the absolute proportion of relatives affected, 25% of case-relatives reported having IBS compared to 12% of control-relatives ($p<0.05$). Furthermore, the magnitude of familial aggregation did not vary by gender of the proband with males and females being equally likely to have an affected relative or set of relatives. Although confidence intervals overlapped, there was a trend for the strength of aggregation to be greatest among probands with diarrhea, followed by constipation, and then mixed bowel habits. Prior intestinal infections, abuse, and depression or anxiety were more common among cases than controls, and among affected relatives than unaffected relatives. The overall prevalence of these risk factors were 9% of affected relatives reporting a prior infection (v. 5% among controls), 35% reporting abuse (v. 25%), and 44% reporting depression or anxiety (v. 22%). Thus, a family member of an individual with IBS is 2–3 times more likely to have IBS, familial clustering is present irrespective of predominant bowel pattern, and the known environmental risk factors for IBS are also common in IBS families.

Study of the pattern of IBS transmission through families has yielded additional interesting observations. A recent study of children with functional gastrointestinal disorders (FGIDs),—but not IBS exclusively— their parents, and their child-aged siblings was performed and it showed that all mothers, fathers, and siblings of cases were more likely to be affected with another FGID than matching control-relatives.⁸ Mothers were the most likely to have a FGID (49.6% case-mothers v. 21.4% control-mothers, $p < 0.05$), followed by their child-aged siblings (26.4% v. 17.6, N.S.), then fathers (13.6% v. 9.3%, N.S.). In contrast, our study of adult patients with IBS showed that adult-aged case-siblings had the highest risk of concurrent IBS, followed by their adult-aged children, and then parents.⁷ Although female relatives were more likely to be affected with IBS, both genders were still at risk for IBS compared to control- relatives. When formal segregation analysis was performed to determine whether the pattern of transmission of IBS through pedigrees is consistent with Mendelian models (e.g. autosomal dominant, recessive, X-linked, etc.), IBS transmission was not consistent with the sporadic model, meaning IBS appeared consistently in families and in parents, arguing against random mutations causing IBS.⁹ More importantly, there was general lack of convergence of the data with segregation analysis. This finding suggests that IBS does not result from a single, major locus, that there was incomplete penetrance, or that IBS could be the result of genetic and environmental factors. The findings are indicative of an underlying genetic basis for IBS.

Although IBS appears to run in families, the previously cited studies suggest that there may be individuals with “sporadic” or non-familial IBS as well as individuals with a familial form of IBS. This observation begs the question as to whether there are clinical characteristics suggesting a distinct mechanistic basis for the sporadic and familial forms of IBS. Genetic diseases may present at an earlier age or present with a more specific form of disease (e.g. colon cancer). Our study found that cases with a stronger family history of IBS had more severe pain, had concurrent fibromyalgia, heartburn, asthma, and reported symptoms of loose stools, urgency constipation, and pain compared to those with less of a family history of IBS ($p < 0.05$).¹⁰ Age of onset was not predicted by family history of IBS thus demonstrating that patients with a family history did not experience IBS symptom onset at a younger age than patients without a family history of IBS. Although at a univariate level of analysis, somatization level, and personal or family history of psychiatric history or abuse were more common among individuals (probands and relatives) with IBS, these factors were not predictive of familial IBS with univariate or with multivariate analyses, suggesting that familial clustering was not related to psychological or psychiatric disease. Kanazawa, et al. has shown that among IBS patients reporting a parental history of bowel problems, these individuals exhibit higher levels of psychological distress.¹¹ These studies suggest that familial forms of IBS are characterized by greater pain severity and greater comorbidity including psychological distress.

Twin studies also support the concept that IBS may be a complex disorder with genetic as well as environmental contributors. To date, there have been at least five twin studies of IBS or functional bowel disorders that estimate that the genetic liability ranges between 1–20% and heritability estimates ranging between 0–57% (Figure 2).^{12–16} In all but one study, the concordance rates for monozygotic twins (who are genetically identical) were higher than the concordance rates for dizygotic twins, suggesting an underlying genetic etiology. Nonetheless, Mohammed, et al. found that concordance rates for monozygotic and dizygotic twins were similar for IBS using a validated questionnaire and the Rome II diagnostic criteria to make the diagnosis of IBS, thus arguing that genes are not a major factor in IBS development, and certainly not a major gene with a strong effect. Studies with twins reared apart, which would permit greater discernment of the influence of different environments in genetically identical twins, are unfortunately lacking.

Heritability (h^2) is another statistical estimate to quantitate the relative genetic contribution to a trait, relative to its environmental contributors. Heritability is the amount or proportion of phenotypic variance of the disease of interest in the population that is inherited through genetic factors. The twin studies show that the heritability estimates range from 0% in the British Twin Study, 22% in the Minnesota Twin Study, 48% in the Norwegian Twin Study, to 57% in the Australian Twin study (Figure 3). Using data collected from families and not twin pairs, when the IBS-Rome criteria were converted into a quantitative trait based on number of Rome symptoms endorsed and severity, the heritability estimates for IBS ranged from 0.19–0.35, depending on the weighting factors for each score. In summary, these studies suggest that the genetic contribution to IBS development is reasonably high and comparable to other diseases for which a genetic basis has been found.

Environmental factors and familial IBS

Despite the consistent observation that IBS clusters in families, this could still be explained by shared environmental contributors, or less likely, individual environmental exposures. Individual environmental contributors that are not likely to be shared among family members or across generations will not be discussed in detail in this review. These exposures include early and later life experiences such as nasogastric tube placement at birth,¹⁷ other painful stimuli experienced during infancy, maternal separation,¹⁸ socioeconomic status,^{19, 20} military deployment,²¹ and microflora.²² These individual environmental factors are still important to potentially include when gene-environment interactions may be required for disease development. This section will discuss shared household exposures that could represent an alternative mechanism besides an underlying genetic basis for the familial aggregation observed in the families of patients with IBS. Environmental exposures that could have been shared between multiple family members include verbal abuse, physical abuse, sexual abuse, shared household stressor/s (e.g. ill family member, unemployment, catastrophe, etc.), parenting style, and learned illness behavior.

Verbal, physical, and sexual abuse during childhood has been reported to be more common in patients with IBS than in matched controls in several studies. Up to 50% of patients with IBS may report a history of lifetime victimization.^{6, 23–26} The mechanism by which abuse is associated with, or possibly leads to development of IBS may be the result of psychological factors rather than a fundamental change in gastrointestinal motor and sensory function. Heitkampker et al. has shown that among those with IBS, few differences were observed in characteristics compared between women with and those without an abuse history.²⁷ Furthermore, when four groups of patients with and without IBS and with and without sexual abuse histories had rectal distension studies performed, although IBS again reported greater sensitivity to rectal distension, sexual abuse did not attenuate results.²⁸ Ringel, et al. has also recently shown that the presence or absence of abuse does not alter rectal sensation or lead to increased rectal pain sensation.²⁹ In contrast, a population-based study found that although childhood abuse was associated with IBS, the abuse was no longer associated for IBS when neuroticism was accounted for and included in the analyses.³⁰ In the only family study examining the role of abuse, our group has shown that in family relatives, the association between abuse and IBS disappeared after inclusion of somatization in the multivariate model. This suggests that either somatization leads to over-reporting of abuse, or perhaps more likely, abuse leads to somatization that ultimately results in IBS symptom development and reporting.⁷ Furthermore, as the majority of patients with IBS report no abuse history, abuse is clearly not required for the development of IBS. The familial clustering of IBS is unlikely to be explained by shared household exposure to an abuser, as the prevalence of abuse is the same among familial and non-familial, sporadic IBS.¹⁰

Besides household exposure to abuse, other shared stressors experienced in a family environment, particularly during childhood, could include adverse life events such as loss of a parent or close relative, significant illness in a household relative, singular or recurrent unemployment, and natural disasters. However, adverse childhood events appear very common—approximately 60% of 17,000 adults from an HMO reported one or more events during childhood, and no secular trends were observed across four birth cohorts.³¹ Another study specifically comparing the role of early adverse life events among IBS patients and controls with respect to salivary cortisol measurements before and after a visceral stressor found that early adverse life events were present in nearly 50% of both patients with IBS as well as their matched controls, and that IBS was equally common among individuals reporting adverse life events as compared to individuals reporting no early life events.³² Although cortisol levels were higher among individuals reporting adverse childhood events compared to those without early events, IBS patients did not have different salivary cortisol responses to stress than controls, and there was only a trend for an interaction between IBS patients who had reported life events and higher cortisol levels compared to controls ($p=0.056$). Furthermore, although adverse life events appear to be common across time and thus, possibly across generations, they are unlikely to be shared across multiple generations making the hypothesis that they could contribute to familial clustering of IBS less viable.

Besides childhood or early adulthood exposures and stressors, others have suggested that the familial clustering of IBS may be due to learned illness behavior modeled from parents. Whitehead et al. surveyed a sample of the general population in metropolitan Cincinnati and found that individuals with IBS symptoms exhibited somatic behavior (e.g. reporting more complaints, consulting physicians for minor complaints) but importantly, reported being given gifts or special foods as children during illness—findings not found in those in acute diseases such as peptic ulcer patients and the asymptomatic general population.³³ Another study also confirmed that patients with IBS were more likely to miss school and have more doctor visits as children than individuals without IBS, suggesting that their parents paid greater attention to their illnesses reinforcing chronic illness behaviors.³⁴ Levy et al. conducted an interview study of mothers with IBS and their children and compared them to mothers without IBS and their children.³⁵ She found that children of mothers with IBS have more gastrointestinal as well as non-gastrointestinal symptoms and have more school absences and physician visits. The investigators found that mother-IBS status was independent from maternal solicitedness (reinforcement of illness behavior) where parent-IBS status influenced children's perceptions of symptom severity but not their perception of the seriousness of gastrointestinal symptoms, whereas parental solicitedness appeared to influence the children's reporting of seriousness of symptoms but not severity. Ultimately, the study supported the role of learned illness behavior, although the authors could not distinguish genetic and environmental contributors to gastrointestinal symptoms.

In summary, shared household environmental factors—whether abuse, other early adverse life events, or learned illness behavior from parental modeling—could explain a subset of cases with IBS, but the degree to which they contribute to familial clustering of IBS still remains to be fully elucidated.

Genetic diseases that mimic IBS

One of the great challenges of studying the genetics of IBS is that there are a number of disorders with symptoms similar to IBS, and a group of these may also have an underlying genetic basis. These diseases include inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis) and celiac sprue. These genetic traits may also co-exist with IBS-- lactose or fructose intolerance, for example—whose presence does not necessarily preclude an IBS diagnosis. As these disorders are not always ruled out prior to inclusion in family studies,

there will always be some degree of uncertainty regarding the potential role of these disorders in the familial aggregation of IBS. Despite this concern of another genetic disorder mimicking IBS, we found that in our group of over 500 IBS cases that their IBS diagnoses endured over inflammatory conditions after extensive chart review as well as serological testing for celiac sprue.⁷ Celiac sprue was found in only 1% of IBS cases and in a comparable proportion of controls. When Villani et al. screened loci associated with Crohn's disease and ulcerative colitis in this sample, IBD loci were not observed in the IBS group.³⁶ Similarly, the prevalence of lactase nonpersistence was no different between IBS cases and their controls (15% v. 14%,³⁷ suggesting that this autosomal recessive trait is unlikely to explain IBS let alone explain the familial aggregation of IBS. Nonetheless, as a mimicker, testing for and adjustment for lactose intolerance, inflammatory bowel disease, and celiac disease may be necessary in gene studies of IBS.

In addition to gastrointestinal diseases, the genetics of other non-gastrointestinal disorders such as psychiatric diseases and traits may be important to account for in family studies of IBS as psychiatric disorders are common in patients with IBS and select antidepressants can be used to treat IBS. A number of studies have shown that there is a link between IBS and psychiatric illness, including in families. Sullivan, et al. reported that among outpatients receiving their first diagnosis of IBS, the prevalence of depression among blood relatives was higher than in controls (5.7% v. 1.8%, $p<0.05$), at a level comparable with a group of individuals with major depression (5%).³⁸ Although the proportion of relatives with depression was higher in IBS patients, the numbers were still quite low, but the authors argue that self-report of family history is less reliable and likely represents an underestimate of the true prevalence of depression. Woodman, et al. conducted interviews of relatives of patients with IBS and patients who had undergone a laparoscopic cholecystectomy and found that the relatives of IBS patients were more likely to report depressive disorders (33.3% v. 17.3%, $p=0.05$) and anxiety disorders (41.7 v. 18.7, $p<0.05$), but not somatoform (2.1 v. 1.8%, $p>0.05$) or substance use disorders (18.8 v. 32.0%, $p>0.05$).³⁹ Hudson, et al. performed a similar study interviewing probands with and without major depressive disorder (MDD) and found that IBS was more common in relatives of probands with MDD than in relatives of probands without MDD (16 v. 7%). In short, there has been suggestion that IBS is part of a larger genetic psychiatric disorder. However, some could argue that because psychiatric co-morbidity is related to health-care seeking but not a common feature in community IBS,⁴⁰ that it is unlikely that a broader psychiatric trait is the heritable component in IBS. Our large family case-control study did not find that a personal history of psychiatry disease, a family history of psychiatric disease, or a family history of alcohol abuse was predictive of familial IBS.¹⁰ And as discussed in the next section, we did not observe that common genetic variants associated with mood disorders were associated with IBS in the absence of psychiatric disease.⁴¹ Thus, although it is possible there is a genetic variant responsible for a psychiatric trait linked to IBS, there is likely a separate genetic and biological mechanism to explain the remaining symptoms of IBS.

Candidate Gene and Pathway Studies

To date, nearly 60 genes have been evaluated to determine whether specific genetic variants may be associated with IBS. The genes, the genetic markers, the findings, and references for these studies are summarized on Table 1. The genes studied lay in the following main pathways: serotonin, adrenergic, inflammation, intestinal barrier, and psychiatric. The genes studied were selected because of their proteins' putative role in gastrointestinal motor or sensory function or because of their potential role in resistance or response to microbial organisms. As gastrointestinal motility and sensation are abnormal in a subset of IBS patients, infection is a risk factor for IBS development, and antibiotic therapy can attenuate IBS symptoms, the genes encoding proteins and peptides related to gastrointestinal function

pose an attractive target of study. Because the number of genetic markers and genes is too great to review in entirety, this section will focus primarily on genetic pathways and positive findings reported by investigators.

Serotonin has been well studied because of its presence in the intestinal tract and brain. Over 95% of the body's serotonin is located in intestinal enterochromaffin cells, but this neurotransmitter is best known for its effect on mood. Selective serotonin reuptake inhibitors (SSRIs) are one the most effective anti-depressant therapies available. Furthermore, serotonin receptor agonists and antagonists are known to accelerate and slow down gastrointestinal transit and positive impact IBS symptoms.^{42, 43} 5-HTT LPR--for serotonin transporter linked polymorphic region—is the best studied functional variant in the psychiatric and IBS field. Eleven candidate gene association studies and a meta-analysis have been published, largely demonstrating no link between this variable number tandem repeat (VNTR) polymorphism and IBS and its subtypes.⁴⁴ In contrast to the psychiatric literature in which a number of studies suggest gene-environment interactions between this variant and abuse or other stressors, no similar interaction was seen between this variant and environment factors such as abuse, parental psychiatric disease, and gastrointestinal infection.⁴⁵

In addition to studies of other genetic variants on the serotonin transporter gene (*SLC6A4*), several studies have examined functional SNPs on the genes encoding serotonin receptors. These genes that encode various receptor subtypes include: *HTR2A*, *HTR3A*, *HTR3B*, *HTR3C*, and *HTR3E*. Three studies had positive findings. One study found that the *HTR3A* -42C>T C/T genotype was more common in IBS-D patients.⁴⁶ Unfortunately, this finding was not replicated in a second cohort. In contrast, the *76G>A SNP on the *HTR3E* gene was found to be associated with IBS-D in two separate cohorts.⁴⁶ This finding is intriguing because the 5-HT_{3E} receptor is expressed in colon, small intestine, and stomach and *in vitro* studies show that there is increased expression of 5-HT_{3E} subunits and thus may have direct effects on the function of 5-HT₃ receptors.⁴⁷ Fukudo et al. studied the 386A>C polymorphism on the *HTR3B* gene and found that regions of brain activation differed between AA subjects and AC and CC subjects.⁴⁸ Our group has recently performed a comprehensive study of over 20 serotonin-related genes in 968 cases and controls and have observed the following associations: 1) 27 SNP associations on 9 genes with IBS with several associations on *TDO2*, *HTR2A*, and *HTR7*; 2) 32 SNPs on 15 genes with IBS-C with multiple associations on *HTR4* and *HTR7*; 3) 26 SNPs on 7 genes with IBS-D with multiple associations on *HTR2A*; and 4) 32 associations on 9 genes with multiple associations on *TPH2*, *DDC*, *TDO2*, *HTR1E*, *HTR2A*, and *HTR7*.⁴⁹ Thus, there are several lines of evidence to suggest that genes involved with serotonin processing are important in the pathophysiology of IBS.

Genes encoding intestinal barrier proteins have also been studied because of a subgroup of IBS patients whose symptoms began after an acute gastroenteritis, known as post-infectious IBS (PI-IBS). Villani et al. conducted an extensive study utilizing the Walkerton Health Study (WHS), a population cohort created after contamination of a municipal water supply in Walkerton, Canada that resulted in a large outbreak of acute *E. Coli* 0157:H7 and *C. jejuni* gastroenteritis with over 2300 developing acute gastroenteritis.⁵⁰ This cohort has undergone clinical assessments as well as intensive surveys to define past and current health and has been followed longitudinally to provide a unique resource to better understand the epidemiological features of PI-IBS. In this study, the investigators selected 79 functional variants in 51 candidate genes that either encoded proteins involved in intestinal epithelial barrier function, innate immune response, the serotonin pathways, as well as other genes postulated by others to be potentially associated with IBS, and tested these variants in 228 cases with PI-IBS and 581 controls. Four of the SNPs were associated with PI-IBS. Two

variants were on the *TLR9* gene encoding the toll-like receptor 9; one was on *CDH1* gene encoding the tight junction protein, cadherin; and one variant was on *IL6* which encodes the cytokine, interleukin-6. Fine-mapping was then performed with selection of additional SNPs in these 3 genomic regions including functional SNPs associated with inflammatory conditions, non-synonymous SNPs reported in dbSNP with minor allele frequencies >1%, SNPs disrupting transcription-factor, microRNA or enhancer binding sites, SNPs located in regulator regions, and tagging SNPs to cover the remaining regions of the three genes (defined as 10kb upstream and 10kb downstream of coding sequence). When multiple logistic regression to identify risk factors for PI-IBS was performed again, now including the 3 candidate polymorphisms from *TLR9*, *IL6*, and *CDH1*, the original risk factors (e.g. younger age, female gender, etc.) as well as these three genetic variants were found to be independent risk factors for development of PI-IBS. These findings appear to be specific to PI-IBS, because when the genetic variants were re-tested in a separate cohort of non-PI-IBS cases and controls, these findings were not reproduced.³⁶

In addition to the genes cited above, other genes in the inflammation pathway have been studied because of reports of cytokine abnormalities in patients with IBS. *IL10* is the gene that has been studied by three groups. Gonssalkorale et al. tested one SNP -1082G>A and found that IBS patients were less likely to have the high producer genotype.⁵¹ Van der Veen and colleagues subsequently observed no association between the same SNP and IBS, as well as no association between the -819C>T SNP and IBS.⁵² Villani et al. noted an association between two SNPs on *IL10* with non-infectious IBS (-592A>C, -1082G>A).³⁶ With further fine-mapping, 16 SNPs on the *IL10* gene were genotyped and five additional SNPs were found to be associated with non-infectious IBS. Three of the five new associations could be explained by linkage disequilibrium with the two original variants, but two variants were still associated with non-infectious IBS suggesting that genetic variation in the *IL10* promoter region may lead to IBS susceptibility. Nonetheless, the inconsistency in findings between study populations, particularly over the -1082G>A polymorphism, suggests that additional confirmatory work on the *IL10* gene and cytokine is needed.

Because depression, anxiety, and somatoform disorders have been reported to occur in up to 94% of IBS patients,⁵³ our group was interested in evaluating the relationship between functional SNPs that have been consistently associated with psychiatric disorders and clinical traits such as mood disorders and pain sensitivity. To this end, ten SNPs on eight genes (*FKBP5*, *COMT*, *NPY*, *BDNF*, *ANKK1*, *DRD2*, *OPRM1*, *FAAH*) were evaluated.⁴¹ None of the ten tested SNPs were observed to be associated with IBS overall. However, the *COMT* Val158Met variant was associated with IBS-C (OR=1.81, 95% CI: 1.01–3.25), the *OPRM1* 118A>G variant was associated with IBS-M (OR=1.57, 95% CI: 1.06–2.30) and IBS-D in females (OR=1.69, 95% CI: 1.00–2.85), and the *BDNF* Val166Met SNP was associated in IBS individuals with a psychiatric disorder. These findings are of interest as the *COMT* variant has been linked to anxiety, obsessive-compulsive disorder, panic disorder, and cognitive performance^{54–56} while the *OPRM1* variant has been linked to pain sensitivity, opioid dependence, and social sensitivity.^{57, 58} The *BDNF* variant has also been linked to emotional reactivity and post-traumatic stress disorder, mood disorders, and schizophrenia.^{59–61}

In conclusion, genes *HTR2A*, *HTR3E*, *IL10*, *IL6* and other genes are intriguing potential candidate genes for IBS (Figure 4). Furthermore, distinct genes—*IL6*, *CDH1*, and *TLR9*—may represent susceptibility loci for post-infectious IBS, with genetic studies suggesting that there is a different genetic basis for sporadic, non-infectious IBS and post-infectious IBS. But clearly, the role of these genetic variants in IBS development still bears further replication in other patient cohorts, as well as confirmation through additional clinical and laboratory testing.

Endophenotypes in IBS

Clinical disease can be the result of an aberrant single physiological pathway, but can also be the result of multiple abnormalities in several biological pathways. In the latter case, understanding and discovering the individual pathophysiological mechanisms that result in disease presentation can be difficult, and can be even more difficult if the disease has heterogeneous clinical features that vary from individual to individual. The term, “endophenotype” originated in the psychiatric literature with the idea that an objective, measurable, and ideally reproducible phenotype of a more abstract or complex clinical phenotype would be more closely related to an underlying biological process. Use of endophenotypes in research implies that the complex biological processes causing disease are more easily discoverable if study of the disease can be parsed out into individual, smaller components. Endophenotypes may be a biomarker, or may be referred to as an *intermediate phenotype* or subclinical trait. In genetics research, endophenotypes should generally have the following characteristics: be associated with illness in the general population, be heritable, co-segregate with illness in families, manifest in an individual irrespective of whether the disease is active or inactive, and be found in affected and unaffected family members of an individual with disease at a higher rate than in the general population.⁶² Because of the lack of objective findings and the clinical heterogeneity of functional gastrointestinal disorders such as IBS, use of an endophenotype strategy in gene discovery for IBS has appeal. Although none have yet been validated as endophenotypes using the Gottesman criteria, at least two testing modalities have been proposed to be potential endophenotypes for IBS: gastrointestinal transit as well as brain imaging with visceral stimulation (Table 2).

Gastrointestinal transit as an intermediate phenotype has been studied extensively by Camilleri and colleagues. This group first postulated that because adrenergic and serotonergic mechanisms modulate gastrointestinal motility, an exploratory study was performed examining these four functional variants-- *ADRA2A* -1291C>G, *ADRC2A* Del 332-325, *GNB3* 825C>T, and 5-HTT LPR-- in 251 patients with FGIDs and healthy volunteers.⁶³ No direct correlation was seen between these 4 genotypes and upper and lower gastrointestinal emptying and transit time, but when interactions between phenotype (e.g. IBS subtype) and genotype were evaluated, several specific interactions were observed. The *GNB3* CC genotype appeared to be predictive of faster gastric emptying among IBS-D patients, the *ADRA2A* CC genotype was predictive of faster gastric emptying among IBS-M patients, and the *ADRA2C* heterozygous genotype was associated with slower gastric emptying among IBS-M patient but faster gastric emptying among IBS-C patients. In a subsequent study, in addition to reporting associations with IBS phenotypes (also summarized in Table 1), this group studied the role of the same four genetic markers and rectal compliance and pain sensation and found an association between 5-HTTLPR LS/SS and increased pain sensation and rectal compliance.⁶⁴ Besides these genetic markers, this group evaluated the role of *FAAH* 385C>A in a group of 482 individuals with FGIDs (predominantly IBS patients) with the underlying hypothesis that because cannabinoid receptors are located on brain stem, gastric, and colonic neurons, functional variants that affect endocannabinoid metabolism could affect gastrointestinal motility and/or sensation, and therefore potentially explain IBS-type symptoms.⁶⁵ They did find that the A allele was associated with IBS-D and IBS-M ($p<0.05$) as well as accelerated transit in patients with IBS-D. In another study, Camilleri et al. proposed that 20 SNPs on the *NPSR1* gene, which encodes a receptor for neuropeptide S which is localized in gut enteroendocrine cells, could potentially play a role in modulated gastrointestinal motor function and found that four SNPs were associated with colon transit time, with significance that persisted after false detection rate correction for multiple tests.⁶⁶

The above studies suggest that the genetic mechanisms for gastrointestinal transit may be specific to IBS subtype. In addition to the previous studies evaluating a mixed group of IBS patients with subanalysis of IBS subtypes, other studies have looked at isolated subgroups. One study of IBS-C patients and seven variants in genes encoding cholecystokinin (*CCK*), *CCK_A* receptors (*CCKAR*), and *CCK_B* receptors (*CCKBR*) found that the intronic 779C>T polymorphism appeared to be associated with delayed gastric emptying in IBS-C patients, but not associated with small intestinal or colonic transit.⁶⁷ A more recent study evaluated variations in genes controlling bile acid absorption, processing, and metabolism with colon transit in a clinical trial evaluating the effects of sodium chenodeoxycholate (CDC) on colon transit and symptoms in patients with IBS-C.⁶⁸ Sixteen non-synonymous SNPs on 7 genes (*NROB2*, *SC10A2*, *KLB*, *FGFR4*, *OST α* , *OST β* , *CYP7A1*) were genotyped and analyzed to determine whether they predicted colon transit time in 36 patient with IBS-C. One SNP on the *FGFR4* gene was found to be associated with filling of the ascending colon ($p=0.015$) and borderline associations between a SNP on the *CYP7A1* gene and colon transit ($p=0.08$). The same investigator has also reported an association between rs17618244 on the *KLB* gene and colon transit time in healthy volunteers as well as those with all IBS subtypes.⁶⁹

Fewer studies have been published regarding the role that genetic variants play in modulating brain activation and processing of visceral stimuli. The only paper published as a full manuscript is a study from Fukudo et al. evaluating the role of the 5-HTT LPR polymorphism in brain processing of rectal stimuli by rectal barostat.⁷⁰ The investigators postulated that since serotonin neurons in the brain are important in mood as well as anxiety-related behaviors, that 5-HTT LPR could potentially predict activation of prefrontal-limbic circuits. Specifically, they hypothesized that the s allele (resulting in lower transcription of the serotonin transporter, leading to greater synaptic quantities of serotonin) could lead to greater activation of the anterior cingulate cortex (ACC) and amygdala. The investigators found that individuals (not IBS patients) with the s/s genotype were more likely to activate left ACC, right parahippocampal gyrus, and left orbitofrontal cortex (OFC) on positron emission tomography (PET) imaging than those bearing the l allele. Since these regions are important in central emotional processing, these findings suggest that this variant may also be relevant in brain activation after colorectal distension in patients with IBS. Labus, et al. reported similar findings—that the s/s genotype appears to result in altered activation of brain regions regulating emotional arousal.⁷¹ In contrast to l carriers who exhibited the expected negative connectivity between the sACC and the amygdala, s/s carriers lacked the feedback inhibition of the amygdala, which they postulated could result in magnified perception of visceral sensation and thus, represent a “vulnerability factor” for IBS. The findings from these two studies suggest the 5-HTT LPR, although not a risk factor for the clinical IBS phenotype, could represent a susceptibility factor for components of IBS such as central processing of visceral events.

In addition to studies of the much-studied 5-HTT LPR variant, two additional variants have been studied in the context of brain processing. Fukudo, et al. subsequently genotyped the rs1176744 polymorphism on the gene encoding the 5-HT_{3B} receptor (*HTR3B*) using similar methodology as the previous study and found that those with the AC or CC genotype demonstrated more activation of the right amygdala, left insula, and left OFC—regions controlling negative emotion-- than AA subjects.⁴⁸ Truong, et al. used a different strategy to evaluate amygdala-based responses by measuring acoustic startle response by threats (fear potentiation [FP]) and prepulse inhibition [PPI] in relation to the *COMT* gene, which encodes the catechol O-methyltransferase enzyme, and important regulator of synaptic dopamine levels.⁷² This group found that there was an interaction between genotype, diagnosis (IBS, fibromyalgia, controls) and threat condition where Met carriers in patients showed enhanced fear potentiation when faced with imminent threat. The authors speculate

that reduced synaptic dopamine in these individuals impair downregulation of amygdala-based startle responses that may lead to hypervigilance to symptoms.

The Future of Genetic Studies in IBS

The field of genetics is rapidly evolving, with technological advances making it increasingly possible to identify common and rare variants on genomic DNA. Current approaches to gene discovery range considerably from the established candidate gene association studies, to the newer genome-wide association studies (GWAS), to newest techniques that involve deep sequencing to identify less common variants. Although the candidate genes have been studied in IBS, the newer methods have not yet been applied to the study of IBS for a number of reasons and limitations. Ultimately, the greatest constraint on IBS gene discovery is the IBS phenotype. IBS is a heterogeneous, unstable disorder, without a well-defined molecular pathway or established biomarkers whose development is clearly multifactorial. Twin studies suggest that there are genes of modest effect that in part explain IBS, but environmental exposures are clearly important in determining the clinical manifestations of IBS. The importance of these environmental factors—such as early or childhood trauma or stress—cannot be ignored as they may be crucial components to IBS vulnerability.

Though twin studies suggest a modest contribution of genetics to IBS and other functional disorders, such studies are limited by the same concerns regarding heterogeneous or even vague disease definitions. Although there does not appear to be a single or dominant Mendelian gene causing IBS, the fact that IBS clusters in families and through multiple generations suggests that there is likely a heritable component to IBS. Nonetheless, future genetic studies will need to study well-characterized, homogeneous groups, or subgroups, of IBS patients. Based on the candidate gene studies, it appears that there may be a different molecular basis for constipation versus diarrhea, sporadic IBS versus post-infectious IBS, and perhaps even for anxiety-associated IBS versus non-anxiety-associated IBS. In addition to studying IBS clinical phenotypes, validated endophenotypes—whether gastrointestinal transit, brain imaging, or another modality such as visceral sensation measures—will provide a complementary approach for successful gene identification. Because environment clearly impacts IBS development and symptom manifestation, these gene-environment interactions should be included in analyses of future genetic studies of IBS. Similarly, studies of epigenetics—environment-induced DNA methylation or histone modification that are heritable but do not result in DNA sequence changes—have not formally been performed but perhaps should be evaluated in future IBS genetic studies. Although genetic studies of IBS need not be family-based and can certainly be performed utilizing information collected from unrelated cases and controls, families represent a unique opportunity to discern the genetic and environmental contributors to the development of IBS. Much work still remains to be done in the field of IBS genetics, presenting an exciting opportunity to make great strides in our understanding in the underlying mechanisms of IBS.

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Figure 1.

Gene-environment paradigm in IBS development. A gene-environment paradigm supports the importance of both genes and environment in the development of IBS for both familial and sporadic IBS. A number of combinations of individual genetic and environmental risk factors are possible, with each specific combination resulting in specific alterations in gastrointestinal motor and sensory function, and ultimately symptom presentation and the final clinical phenotype.

Figure 2.

Familial aggregation of IBS. Fifty percent of cases with IBS will have at least one other family member with IBS, but the overall proportion of first-degree relatives with IBS is 25%. Overall, case-relatives are two to three times as likely to have IBS than control-relatives.

Figure 3. Estimated genetic liability and heritability in IBS twin studies. Five twin studies have evaluated the concordance of IBS between twin pairs. Genetic liability of IBS has been estimated to range between 1–20% and heritability estimates in the best fit model ranged between 0–57%.

Figure 4.

Summary of positive gene associations, by IBS type and subtype. Positive gene associations that were shown in Table 1 are summarized by IBS phenotype. Some genetic associations are unique to specific IBS types and subtypes, where others were shown to overlap between IBS subtypes.

Table 1

List of candidate genes tested in IBS patients

Gene	SNP RSID#	Variant	Associated with IBS?	Reference
Serotonin pathway genes				
<i>SLC6A4</i>	Rs4795541	5-HTTLPR (44bp ins/del)	No LS, LL α IBS-C	36, 44, 50, 64
		STin2 VNTR	No	73–75
	rs25531	-	G allele	75
	Rs3813034	G>T	No	50
<i>HTR2A</i>	rs6313	102T>C	No	50, 76
	rs6311	-1438G>A	No	50, 76
	rs6314	H452Y	No	50
<i>HTR3A</i>	-	-42C>T	CT α IBS-D	46
	-	-25C>T	No	46
	-	*70C>T	No	46
	-	*503C>T	No	46
<i>HTR3B</i>	-	386A>C	AC/CC	48
<i>HTR3C</i>	-	489C>A	CC α IBS-D	77
<i>HTR3E</i>	rs62625044	*76G>A	GA α IBS-D	46
	-	*115T>G	No	46
	-	*138C>T	No	46
	-	-189A>G	No	46
<i>TPH1</i>	rs1800532	218A>C	No	50
	rs1799913	779A>C	No	50
<i>TPH2</i>	rs11178997	-473T>A	No	50
	rs4570625	-703G>T	No	50
	rs4565946	90A>G	No	50
Inflammatory/Immune pathway genes				
<i>IL10</i>	rs1800896	-1082G>A	A α IBS; No; G α IBS; GA α IBS	36, 50–52, 78
	-	-819C>T	No	52
	rs1800872	-592A>C	No	50
<i>TNFα</i>	-	-308G>A	GA α IBS; No; No	52, 79, 80
	-	-238G>A	G α IBS	79
<i>TGF β1</i>	rs1982073	+869T>C	No	51
	rs1800469	-509C>T	No	50

Gene	SNP RSID#	Variant	Associated with IBS?	Reference
<i>NOD2</i>	rs2066847	Leu1007insC	No	50
	rs2066844	R702W	No	50
	rs2066845	G908R	No	50
	rs2076756	-	No	50
<i>NOD1</i>	rs6958571	ND1+32656*1	No	50
<i>CARD8</i>	rs2043	Cys10Stop	No	50
<i>TLR4</i>	rs4986790	D299G	No	50
<i>TLR5</i>	rs5744168	1174C>T	No	50
<i>TLR9</i> ⁺	rs5743836	-1237T>C	T α PI-IBS	50
	rs352139	2848G>A	A α PI-IBS	50
<i>CD14</i>	rs2569190	-159T>C	No	50
<i>NFKB1</i>	rs28362491	-94delATTG	No	50
<i>ATG16L1</i>	rs2241880	T300A	No	50
<i>PTGER4</i>	rs4495224	-	No	50
	rs6313763	-	No	50
	rs9292777	-	No	50
<i>IRGM</i>	rs4958847	-	No	50
	rs13361189	-	No	50
<i>NKX2-3</i>	rs10883365	-	No	50
	rs7078219	-	No	50
<i>PTPN2</i>	rs2542151	-	No	50
	rs2847297	-	No	50
<i>IFNA</i>	-	874T>A	No	80
<i>TNF</i>	rs1800629	-308G>A	No	50
	rs1799724	-857C>T	No	50
	rs1800630	-863C>A	No	50
	rs1799964	-1031T>C	No	50
<i>IL1A</i>	-	-889T>C	No	79
<i>IL1B</i>	rs1143627	-31C>T	No	50
	rs1143634	F105F	No	50
	rs16944	-511C>T	No	50, 79
	-	+3962C>T	No	79
<i>IL1R</i>	-	Pst-I 1970C>T	C α IBS	79

Gene	SNP RSID#	Variant	Associated with IBS?	Reference
<i>IL1RA</i>	-	Mspa-I 11100T>C	No	79
<i>IL4</i>	rs2243250	-590C>T	No; C α IBS	50, 78
	-	-33T	T α IBS	78
<i>IL4R</i>	rs1801275	Q576R	No	50
	rs1805015	S503P	No	50
<i>IL6</i>	rs1800795 ⁺	-174G>C	C α PI-IBS; G α IBS	50, 79, 80
	-	nt565	No	79
	-	-1082A>G	No	80
	-	-819T>C	No	80
	-	-592A>C	No	80
<i>IL6R</i>	rs4537545	-	No	50
	rs8192284/	D358A	No	50
	rs2228145			
<i>IL7R</i>	rs6897932	T244I	No	50
<i>IL8</i>	rs4073	-251T>A	No	50
<i>IL12B</i>	rs10045431	-	No	50
	rs6887695	-	No	50
<i>IL13</i>	rs20541	R130Q	No	50
	rs1800925	-1112C>T	No	50
<i>IL23R</i>	rs11209026	R381Q	No	50
(3p21)	rs9858542	-	No	50
(10q21.1)	rs224136	-	No	50
	rs224135	-	No	50
(5q31)	rs2188962	-	No	50
Intestinal barrier genes				
<i>SLC22A4</i>	rs1050152	1672C>T	No	50
<i>SLC22A5</i>	rs2631367	-207G>C	No	50
<i>CDH1</i> ⁺	rs16260	-160C>A	A α PI-IBS	50
	rs5030625	-347G>A	No	50
<i>ICAM1</i>	rs5498	K469E	No	50
	rs1799969	G241R	No	50
<i>DLG5</i>	rs1248696	R30Q	No	50
<i>MYO9B</i>	rs1545620	S1011A	No	50

Gene	SNP RSID#	Variant	Associated with IBS?	Reference
<i>ABCB1</i>	rs1045642	3435C>T	No	50
	rs3789243	-	No	50
<i>NR1I2</i>	rs3814055	-25385C>T	No	50
	rs6785049	7635A>G	No	50
<i>LTF</i>	rs7645243	Leu632Leu	No	50
<i>BPI</i>	rs4358188	E216K	No	50
Adrenergic pathway genes				
<i>NET</i>	-	237G>C	No	81
<i>ADRA2A</i>	rs1800035	753C>G	No	50, 64, 81
	rs1800544	-1291C>G	G α IBS-C; CG/GG α IBS-D; No	50, 81, 82
<i>ADRA2C</i>	-	Del 332-335	IBS-C	81
Psychiatric genes				
<i>FKBP5</i>	rs3800373	-	No	41
	rs1360780	-	No	41
	rs9470080	-	No	41
<i>COMT</i>	rs4680	Val158Met	Met α IBS-C	41
<i>NPY</i>	rs16147	-	No	41
<i>BDNF</i>	rs6265	Val166Met	Met α psychiatric IBS	41
<i>ANKK1</i>	rs1800497	-	No	41
<i>DRD2</i>	rs12364283	Ser311Cys	No	41
<i>OPRM1</i>	rs1799971	118A>G	G α IBS-M, IBS-D females	41
Other tested genes				
<i>CCK</i>	rs1800857	779T>C	No	50
<i>CCK1R</i>	-	Intron1 779T>C	C α IBS-C	83
		Exon1 G>A	No	83
	-	266G>C	No	84
	-	8641G>A	No	84
	-	984T>C	No	84
<i>CNR1</i>	-	AAT repeats	Yes	85
<i>FAAH</i>	rs324420	385C>A	A α IBS-D, IBS-M. No	41, 65
<i>GN β3</i>	rs5443	825C>T	No, but possible interaction with GI infection	45, 50, 64, 86-88
<i>NPSR1</i>	rs2609234	-	No	66
	rs714588	-	No	66

Gene	SNP RSID#	Variant	Associated with IBS?	Reference
	rs1963499	-	No	66
	rs2168890	-	No	66
	rs2530547	-	No	66
	rs887020	-	No	66
	rs1379928	-	No	66
	rs323917	-	No	66
	rs323922	-	No	66
	rs324377	-	No	66
	Hopo546333	-	No	66
	rs324396	-	No	66
	rs10278663	-	No	66
	rs740347	-	No	66
	rs324981	Ile107Asn	No	66
	rs727162	Arg241Ser	No	66
	rs6972158	Arg344Gln	No	66
SCN5A		G298S	IBS-D	89

Table 2

List of genes evaluated in gene-endophenotype studies

Endophenotype: Gastrointestinal transit	Endophenotype: Brain imaging
Serotonin genes <ul style="list-style-type: none"> • SLC6A4 Adrenergic genes <ul style="list-style-type: none"> • ADRA2A • ADRA2C Bile acid processing and metabolism <ul style="list-style-type: none"> • NROB2 • SC10A2 • KLB • FGFR4 • OST α • OST β • CYP7A1 Cannabinoid genes <ul style="list-style-type: none"> • FAAH Cholecystokinin <ul style="list-style-type: none"> • CCK • CCKAR • CCKBR Neuropeptide S <ul style="list-style-type: none"> • NPSR1 Other <ul style="list-style-type: none"> • GN β3 	Serotonin <ul style="list-style-type: none"> • SLC6A4 • HTR3B Dopamine <ul style="list-style-type: none"> • COMT