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Genes and Irritable Bowel Syndrome: Is There a Link?

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Abstract

Advances in genetics and genomics during the past decade, including sequencing of the human genome and DNA sequencing technologies, have made it possible to discover the genetic basis for many diseases. With the discovery of multiple genetic loci for gastrointestinal diseases such as Crohn's disease, some have begun to wonder—Could there be a genetic basis for irritable bowel syndrome (IBS)? This article summarizes the evidence for and against a link between genes and IBS. In addition, a gene–environment paradigm is presented to combine the two opposing hypotheses, as IBS may represent a complex genetic disorder that results from the interaction of several genes and environmental risk factors.

Introduction

Over the past several decades, significant advances have been made in the field of human genetics. One of the greatest achievements has been the successful sequencing of the entire human genome with the Human Genome Project, started in 1990 and completed in 2003. Its primary goals were to determine the sequence of the 3 billion chemical base pairs that make up human DNA and to identify all genes in the human genome. Each gene, by providing the template for the human body's proteins, determines not only how humans look and behave but also how less obvious but very important bodily functions and processes are performed, including the response to food and the environment. In addition to determining our health, the genetic code is an important determinant in the development of disease. The pieces of the genetic puzzle have been identified, but their clinical relevance has yet to be determined. A question of great interest is whether genes and genetics could be responsible for irritable bowel syndrome (IBS), one of the most common gastrointestinal disorders seen by gastroenterologists and primary care physicians alike [1].

This review summarizes the rationale and evidence—in favor and opposing—for an underlying genetic basis for IBS. First, a brief overview of IBS is provided, as it is a clinically heterogeneous disorder with varying diagnostic definitions [2–4,5•]. Second, genetics and genetic terms are summarized to set the contextual stage, and then the data supporting a genetic basis for IBS are discussed in depth. This discussion is followed by a detailed examination of the nongenetic contributors to IBS—the “environmental” risk factors. Finally, a paradigm is presented that blends the two opposing theories—a combination of nature (genetics) and nurture (environment)—that may explain the heterogeneous clinical presentation of IBS.

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A Clinical Overview of IBS

IBS is a common disorder characterized by chronic, recurrent abdominal pain or discomfort that is associated with bowel dysfunction such as diarrhea, constipation, or both. Concurrent symptoms may include bloating or abdominal distention, urgency, and a sensation of incomplete evacuation. Several population-based studies have shown that about 10% to 20% of the general population are affected, including children and adults through a wide age range. Symptoms can begin at any age but typically start in the young adult years [6]. The severity of symptoms may influence an individual's decision to seek medical attention, as IBS is frequently seen by both primary care providers and gastroenterologists. For individuals with typical symptoms that meet Rome criteria for IBS (in the absence of worrisome symptoms such as fever, chills, or blood per rectum), the diagnosis may comfortably be made without laboratory, radiologic, or endoscopic testing [5•].

Even though bowel symptoms are common in the population at large, the underlying pathophysiology of IBS remains poorly understood. Abnormal gastrointestinal motility and brain-gut interactions are thought to play a role in a subset of those with IBS, but they do not explain the symptoms in all patients. Because the exact molecular basis for IBS remains unknown, treatment of symptoms may consist of several families of pharmacologic agents, chosen according to the primary symptom. For example, antispasmodics or visceral neuromodulating agents will be prescribed for those with significant pain, antidiarrheals for those with frequent or loose stools or urgency, and prokinetics or laxatives for those with infrequent or hard stools. Pain-modulating agents may include anticholinergics, selective serotonin reuptake inhibitors, or γ -aminobutyric acid (GABA)-based agents. Antidiarrheal therapy may consist of opioid-based medications (eg, loperamide) but also may include other therapies such as fiber, anticholinergics, cholestyramine (bile-salt binder), or serotonin 5-HT₃ receptor antagonists (eg, alosetron). Treatment of constipation may consist of fiber-based therapy, stool softeners, osmotic agents (magnesium or polyethylene glycol-based), stimulant laxatives, serotonin 5-HT₄ receptor agonists (eg, tegaserod), and agents that affect intestinal chloride ion channels (eg, lubiprostone).

In summary, a wide array of agents with different underlying pharmacologic mechanisms may be used to treat IBS symptoms, but the success of these agents in treating IBS does not provide clear insight into its underlying mechanisms. Research continues to search for the causes of IBS in hope of finding better treatment options and, ultimately, preventing the development of IBS in those without symptoms.

Genetic Concepts and Terminology

Because much has changed in genetic terminology and concepts over the past several years, a brief overview may be helpful. The *genome* refers to all DNA in humans, including its coding genes as well as non-coding regions. The Human Genome Project found that there are 3164.7 million nucleotide bases and the average gene size is 3000 bases; the total number of genes is estimated at 20,000 to 25,000 (www.ornl.gov/hgmis/home.shtml). Individuals share approximately 99.9% of the same genetic code (of which at least 50% consists of “junk DNA”), so a relatively small portion of our genetic sequence explains seemingly large differences among individuals with respect to appearance and overall health. Despite the progress made by the Human Genome Project, the functions of over 50% of discovered genes remain unknown.

Within each gene, there is generally a promoter region and a number of coding exon regions divided by noncoding introns. At the gene level, several forms of genetic variation exist among individuals. These genetic variations may come in the form of an insertion, a

deletion, or a substitution, each of these involving one nucleotide or a number of nucleotides. Common variants described in the genetic literature include single nucleotide polymorphisms, restriction fragment length polymorphisms, and a variable number of tandem repeats. These variations can all be referred to as *polymorphisms* if they are present in more than 1% of the general population. The term *mutation* is generally reserved for rare polymorphisms (present in < 1%) that are clearly associated with causing disease.

When a specific polymorphism is being studied and has been genotyped, this DNA region is often referred to as a *locus*. An *allele* refers to the forms of a genetic locus that may exist. For single nucleotide polymorphisms, there are only two forms of a genetic locus: one inherited from the mother and one from the father. A *genotype* refers to the two alleles that an individual may have inherited from his or her parents. The term *phenotype* is a broader term that applies to the clinical characteristics of an individual. This may be descriptive (eg, eye color) or may be a designation of disease status (eg, colon cancer, affected or unaffected). Although *phenotype* is typically used in a genetic context, a phenotype need not necessarily be genetic in origin, and it may be qualitative or quantitative.

A relatively new concept that has evolved in genetics over the past decade is a shift from studying true Mendelian disorders to studying complex genetic diseases. Mendelian diseases are characterized by rare but functional mutations, which frequently result in dramatic disease (eg, Huntington's disease) that is transmitted through a family in a predictable pattern (eg, autosomal dominant or recessive). Complex genetic diseases are thought to be caused by multiple polymorphisms frequently found in the general population. By themselves they may not result in overt disease, but in combination with each other and with environmental contributors, they will result in disease. These diseases also tend to aggregate in families. An example of this type of gastrointestinal disease would be Crohn's disease, involving the *NOD2/CARD15* gene. Crohn's has been shown to cluster in families, but not to the same extent as a traditional "genetic" disease. It is likely to be the result of several genetic variants and perhaps environmental factors as well.

Because a gene has been identified for Crohn's disease, one might ask whether a gene or set of genes can be found for other gastrointestinal disorders. Could there be a gene causing IBS? The challenge in hunting for a gene is the vast territory of the genome to be covered. Although the cost of genotyping is decreasing, it is still relatively expensive to genotype thousands of markers across the genome, and it is still labor intensive (and therefore expensive) for statistical geneticists to analyze the large amount of data generated. If IBS is a complex genetic disease, identification of a disease susceptibility locus will require a logical methodologic approach and perhaps some luck and ingenuity.

Possible Links Between IBS and Genetics

Family studies of IBS

The possibility of a genetic basis for IBS stems in part from various reports that IBS aggregates or clusters in families—a key characteristic of genetic disorders. Using a billing database from a health maintenance organization, Levy et al. [7] found that children of parents with IBS were more likely to present with abdominal complaints than children of parents without IBS. This study could not assess specifically whether the children were more likely to have IBS, however. Whorwell and colleagues [8] observed that 33% of their IBS patients reported a positive family history of IBS, compared with only 2% of controls matched for age, gender, and social class. A group of general practitioners in Italy observed that a family history of IBS was one of five predictors of a final diagnosis of IBS among patients presenting with recurrent abdominal pain [9]. One population-based study has shown that residents reporting a first-degree relative with IBS were more likely to report

IBS symptoms (OR, 2.5; 95% CI, 1.5–4.2) with adjustment for age, gender, and somatization level [10]. Some caution must be applied in interpreting these family studies, however, because many used proxy reporting and did not collect family history of IBS directly from relatives. Our group has shown that proxy reporting of IBS in families has low agreement, with a κ value of 0.27; both cases and controls tended to underestimate the frequency of IBS in their relatives [11]. By direct survey of first-degree relatives of outpatients with IBS (with controls matched for age, gender, and race), we have confirmed that IBS aggregates strongly in families: case-relatives are more likely to be affected with IBS by Rome criteria (OR, 3.1; 95% CI, 1.6–6.0) [11]. Recurrence risks of specific relatives were highest in parents and siblings, with risks ranging from 3.1 to 4.2, and lowest in children, with risks ranging from 1.4 to 2.4. Because of the small sample size, however, the risks were statistically significant only in mothers and sisters. Persistent aggregation was observed when families were stratified by the number of family members with psychological or psychiatric disorders, suggesting that the clustering of IBS is not due simply to clustering of mental health disease. Another study has shown that familial aggregation of IBS does not appear to be the result of coexisting psychological factors (eg, perception of stress) or psychiatric disorders (eg, anxiety or depression) [12]. This study showed that a family history of bowel problems was an independent risk factor that remained a significant predictor of IBS diagnosis after adjusting for anxiety, depression, and perception of stress.

In summary, several studies using various methods have confirmed that IBS symptoms are more common in relatives of patients with IBS, providing some basis for a potential genetic component. However, these family studies are far from conclusive, as there may be multiple reasons for clustering of disease, including shared environment.

Twin studies

Studies of twins are the classic family-based method to distinguish between genetic and environmental contributors to disease. By comparing concordance rates of monozygotic twins (who share 100% of the same genes and presumably the same environment during upbringing) with concordance rates of dizygotic twins (who share 50% of genes and presumably the same environment), the difference between the concordance rates is used to estimate the genetic liability to disease.

To date, five classic twin studies have been published in IBS, including two from our group [13–17]. On the basis of the concordance rates, the genetic liability is estimated to range from 0% to 20%. The reasons for the heterogeneity in liability are not clear; it may represent IBS prevalence differences by population, or it may be due to methodologic differences with respect to how IBS status was defined and how the information was collected. Nonetheless, the estimates from these studies suggest that there is a genetic contribution for IBS, but it is modest.

In four twin studies, additional modeling of the correlations between members of a twin pair was performed to resolve whether the phenotypic variance observed could be attributed to genetic or environmental components [13,15–17]. Testing a series of models that included additive genetic (multiple small genetic), dominant genetic, shared environmental, or unique or individual environmental components, researchers in 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% in the Minnesota twin study [17], 48% in a Norwegian study [16], and 57% in an Australian study [13], whereas the individual environmental contribution 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. These studies had two major limitations: not all used direct survey of both twins to confirm IBS diagnosis and the definitions of IBS varied. Furthermore, modeling may not have adequately taken into account psychosocial factors and specific environmental risk factors pertinent to IBS and the possible etiologic heterogeneity underlying IBS. Nonetheless, these studies do suggest that there is a genetic basis for IBS, but the genetic effect is not strong.

Candidate gene and pharmacogenetic studies

Candidate genes are specific genes identified by an investigator for study, typically on the basis of a known or hypothesized role of the coded protein in disease pathophysiology. A candidate gene study typically assesses a specific polymorphism or set of polymorphisms. Published candidate gene studies have studied the following genes: serotonin transporter (*SLC6A4*) [18–21], 5-HT_{2A} receptor (*5HT2A*) [22], norepinephrine transporter (*NET*) [18], α_{2A} -adrenergic receptor (*ADRA2A*) [18], α_{2C} -adrenergic receptor (*ADRA2C*) [18], interleukin-10 (*IL10*) [23,24], transforming growth factor- β 1 (*TGF β*) [23], tumor necrosis factor- α (*TNF- α*) [24], β 3 subunit of the G protein (*G β 3*) [25,26], sodium channel 1.5v (*SCN5A*) [27], and fatty acid amide hydrolase (*FAAH*) [28]. Although the 5-HTT LPR polymorphism is the best-studied in IBS patients, a recent meta-analysis has concluded that it is not linked to IBS or its subtypes [29•]. Potential associations have been observed with the *IL10* gene, *TNF- α* gene, *SCN5A* gene, and *FAAH* gene, but these should be examined in separate large patient samples, as false-positive associations are frequently observed in candidate gene studies [30]. Of note, these candidate gene studies can assess the role only of the specific polymorphism studied, not the role of the other 50 to 100 polymorphisms present on the gene. Thus, negative studies typically rule out a role in disease development only for the studied polymorphism, not for the entire gene.

Pharmacogenomics is a field that evaluates the links between genetic variants and drug response. Two pharmacogenomic studies have suggested a potential association between the 5-HTT LPR polymorphism on the serotonin transporter (*SLC6A4*) gene and response to therapy in IBS [31,32]. In diarrhea-predominant IBS patients participating in an alosetron efficacy trial, greater delays in colonic transit occurred with alosetron treatment in L/L homozygous patients than in L/S heterozygous patients [31]. In contrast, Li et al. [32] observed that constipation-predominant S/S homozygotes were more likely to respond to tegaserod, a 5-HT₄ agonist. These different responses to drug therapy suggest that genetics may affect drug efficacy in tangible ways. In summary, a definitive disease-susceptibility gene for IBS has yet to be clearly identified, but some promising candidate gene studies have been performed that bear future study.

IBS Has an Environmental Basis

An environmental basis for IBS could occur through exposure to an environmental risk factor, parental teaching of illness behavior, or both. Many forms of environmental risk factors may exist [33•], but perhaps the most plausible and best-studied environmental exposures include socioeconomic status, abuse, and early childhood trauma. Two studies have demonstrated an association between high childhood socioeconomic status and IBS. Mendall and Kumar [34] evaluated patients in a general practice setting and found an association between IBS and recall of living during childhood at a density of less than 1 person per room. Another study examining the potential role of childhood socioeconomic status on risk of IBS also observed a link between childhood affluence and adult IBS, using data collected from the New Zealand birth cohort [35]. The association was characterized by a near-linear decrease in odds of IBS with each lower socioeconomic class, and adjustment for adult social class did not affect findings. Adult social class was not associated with adult IBS.

Several investigators have reported that over half of patients with IBS may have a history of exposure to abuse [36–38]. Some studies did not differentiate between abuse in childhood and adulthood [39,40], but others have reported a link between childhood abuse and IBS [37,41,42]. However, Talley et al. [43] performed a follow-up population-based study and found that childhood abuse was not associated with adult IBS after adjusting for age, gender, and psychological factors such as neuroticism. In contrast with the other studies, another community-based study found that abuse in adulthood but not in childhood was more common in individuals with IBS, functional dyspepsia, or both [44]. However, abuse was not an independent predictor for IBS after adjustment for psychological and buffering factors in the multivariate analysis. Despite the conflicting data, it does appear that abuse in childhood, adulthood, or both is relevant in the development of adult IBS, but it is not clear that the link with abuse is not explained in part by psychological factors. Furthermore, because many patients with IBS deny abuse exposure, physical or sexual abuse is not likely to explain the development of IBS in all patients.

Others have argued that any form of psychological or physical trauma, particularly during childhood, may result in IBS. One study found that early life trauma may be linked with IBS. Gastric suction at birth was found by multivariate regression to be associated with discharge from a hospital with IBS later in life, and no link was found with other maternal and perinatal confounders [45]. In another study of IBS outpatients, 61% of patients reported an unsatisfactory relationship with their parents and 31% reported parental loss through death, divorce, or separation [46]. Similarly, the animal model for IBS is maternally separated rat pups, which demonstrated increased visceral sensitivity and altered bowel habits, similar to patients with IBS [47]. However, the finding of Bengtson et al. [16] that the lower-birth-weight twin was more likely to develop IBS and at a younger age of onset suggests that prenatal developmental factors may be extremely relevant to the pathophysiology of IBS. In total, these studies suggest that trauma during infancy or childhood may be an extremely important environmental risk factor for the development later in life of functional gastrointestinal disorders such as IBS.

Another topic of great interest in the IBS community is the concept that IBS may be the result of learned illness behavior, with parental teaching or modeling of increased health care seeking. For example, Whitehead and colleagues [48,49] showed that IBS patients were more likely than patients without IBS to report that their parents responded to illness complaints with gifts or privileges and were more likely to recall that their parents demonstrated illness behavior. Similarly, Lowman et al. [50] confirmed the finding of increased parental illness behavior in patients with IBS. In addition to these retrospective studies, several prospective studies have been performed. In the Avon Longitudinal Study of Parents and Children (ALSPAC), a study designed to examine the impact of social, environmental, genetic, and biologic factors on the health and development of children, the investigators identified and compared symptoms and health care seeking for infants aged 0 to 18 months belonging to 73 mothers with IBS, constipation, and abdominal pain consistent with functional gastrointestinal disorders and 154 mothers reporting a history of stomach ulcers [51]. The two groups of mothers—who were comparable with respect to age, social class, education level, marital status, and number of children—showed no differences in the proportion of children with reported health problems (including gastrointestinal symptoms), but the mothers with functional gastrointestinal disorders did bring their children to the doctor more often than the mothers with stomach ulcers ($P < 0.05$), particularly for sniffles/colds but not for more serious symptoms such as high fever, rashes, or wheezing. Maternal psychiatric history and scores on the Edinburgh Post-Natal Depression Scale were comparable between the two groups of mothers, arguing that maternal psychological factors were factors leading to increased health care seeking for their children. The investigators hypothesized that this differing response to common, benign symptoms may have a long-

term impact on the development of habitual illness behaviors, although they did not observe increased vigilance or health care seeking for gastrointestinal symptoms. Nonetheless, this study provides some evidence for differences in health care-seeking behavior among women with and without IBS, and raises a valid question as to whether this early behavior could later become learned by the children themselves.

Other studies have also shown that IBS may be associated with learned illness behavior from parental modeling. Levy et al. [7], using an HMO administrative database, showed that children of a parent with IBS were more likely to have ambulatory care visits for gastrointestinal symptoms (as well as for all causes), and the gender of the parent did not change the findings. Nonetheless, the authors could not exclude alternative explanations such as heritability, effects of family stress, or parental decisions guiding when children are brought to the clinic (ie, the parent's illness behavior is being documented, not the child's). In a subsequent study, the investigators independently interviewed mothers with IBS and their children and mothers without IBS and their children and found that case-children independently reported more gastrointestinal complaints and nongastrointestinal complaints than control children [52]. The investigators found that the gastrointestinal complaints of the children were not explained by the mother's biased perceptions. Parental IBS status did have an independent effect on the child's frequency of symptom complaints, and solicitous responses from parents had independent effects on the child's perception of the seriousness of symptoms.

Although there is strong plausibility behind learned illness behavior in the context of a chronic disorder such as IBS, this theory may specifically apply to those with a positive family history of IBS and those who seek medical attention. Several studies have documented that only 9% to 56% of individuals with IBS seek medical attention [53–57]. The familial aggregation studies suggest that at most, 20% to 50% have a positive family history of IBS, and the affected family member is not necessarily the parent. Interestingly, one Japanese study of consulters and nonconsulters did not observe differences between the groups with respect to the proportion reporting a parent with IBS [12]; this finding seems to contradict the need for parental affectedness in the model of learned illness behavior. Furthermore, using the Abnormal Illness Behavior Questionnaire and Social Learning of Illness Behavior scale, Australian investigators did not observe differences between abnormal illness behavior and aspects of social learning of illness behavior (encouragement, reinforcement, modeling) between consulters and nonconsulters with IBS or functional dyspepsia [58]. In summary, parent-to-child transmission of learned illness behavior may apply only to a subset of patients with IBS, but it is a field that warrants further study.

A Putative Gene–Environment Paradigm

The studies reviewed in this article are not conclusive and cannot yet definitively quantitate the contributions of genetics and environment to IBS. Studies of IBS are complicated in part by the heterogeneity of symptoms and in part by the heterogeneity of risk factors for IBS among patients. Nonetheless, tying the reported studies together, one could postulate that IBS is likely to be an extremely complex genetic disorder that is the result of multiple genes of modest effect as well as environmental risk factors, including trauma. The American Gastroenterological Association has published a technical review summarizing the opinions of experts in the field [1]. This technical review included a paradigm for the factors contributing to IBS pathophysiology. Figure 1 is a modification of this paradigm that includes some factors discussed in this article and indicates those factors that could be influenced by genetics. One would suspect intuitively that genetic alterations in genes that encode proteins affecting gastrointestinal motility or sensation could be involved in IBS development. In addition, alterations in the genes encoding proteins in the immune system

may be relevant in determining who may be susceptible to developing postinfectious IBS. Alterations in genes encoding digestive enzymes (eg, lactase, disaccharidase) could also affect food tolerance. Genetic alterations increasing the risk of depression, anxiety, or somatization—or even personality—may also be relevant in the development of IBS. The paradigm shown in Figure 1 proposes the various combinations of genetic and environmental components that may result in IBS and its variable presentation.

Conclusions

The findings reported in this article suggest that there is indeed a potential link between genes and IBS. The link does not appear to be as strong or absolute as for traditional Mendelian genetic diseases, however, and environmental exposures during an individual's childhood and adulthood may be relevant to the type of symptoms an individual presents with, the severity of the symptoms, and, importantly, when the individual may seek medical attention. Future studies—particularly of families—may be extremely helpful in identifying the relevant genetic and environmental factors that are important in the development of IBS, but only the future will determine whether there is a concrete genetic basis for symptom development and treatment response.

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Figure 1.

Proposed paradigm for the pathophysiology underlying irritable bowel syndrome (IBS). C-IBS—constipation-predominant IBS; CNS—central nervous system; D-IBS—diarrhea-predominant IBS; ENS—enteric nervous system; M-IBS—mixed IBS.