Editorial

The genetics of irritable bowel syndrome—some progress at last?

Eamonn M. M. Quigley

Division of Gastroenterology and Hepatology, Lynda K and David M Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, Houston, Texas, USA

Correspondence to: Eamonn M. M. Quigley, MD, FRCP, FACP, MACG, FRCPI. Division of Gastroenterology and Hepatology, Lynda K and David M Underwood Center for Digestive Disorders, Houston Methodist Hospital and Weill Cornell Medical College, 6550 Fannin St, SM 1201, Houston, Texas 77030, USA. Email: equigley@houstonmethodist.org.

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Irritable bowel syndrome (IBS) is a common disorder characterized by abdominal pain or discomfort that is associated with disturbed bowel function and often accompanied by bloating, distension and difficult defecation (1). IBS has a global prevalence of 2–25%, depending on the criteria used and the population surveyed (2). Sufferers report reduced quality of life, increased rates of school/work absenteeism and physicians' visits (1); impacts that are often underappreciated by health care providers (3). The pathophysiology of IBS remains unclear; however, dysregulation within the brain gut axis, interactions between genotype, psyche, the gut microbiota and the host immune response, as well as gut motor and sensory dysfunction, are believed to play a role (4). Among these, post-infection IBS has emerged as the sole instance where a causative factor can be identified (5).

Every day, clinicians who care for patients with IBS will hear of instances of IBS among parents, siblings and children of IBS sufferers and formal studies of familial aggregation of IBS symptomatology have long pointed towards a possible genetic component to IBS (6-8). However, defining the contribution of genetics in IBS has proven to be far from straightforward. First, given what we know of the impact of early childhood experiences on IBS prevalence and severity (9,10), some would argue that familial aggregation reflects shared experiences and common exposures and not shared genes. Second, IBS is a clinically defined entity which lacks a universal biomarker and presents with a highly variable phenotype (11). It is, indeed, likely that what the clinician currently recognizes as IBS may ultimately be defined as comprising several distinct syndromes; for the very same reason, it is unlikely that a single genetic variant is responsible for the development of IBS. Third, IBS is usually accompanied by a number of psychological and physical co-morbidities which are likely to confound the interpretation of any genetic study. IBS is more likely to be either a polygenic disease in which common variants in a large number of genes interact with environmental factors to produce the clinical manifestations of IBS or to be epigenetic in origin (12).

Considerable effort has been expended, therefore, on the identification of genetic markers that might identify a particular subset of the IBS population or predict response to a certain therapeutic approach. Understandably, given its roles in gut motility, sensation and epithelial physiology, attention focused on the serotonergic system and, in particular, on genetic variations in the serotonin re-uptake transporter (SERT), the membrane protein which mediates the extracellular reuptake of serotonin; thus, regulating its biological functions (13). Specifically, it was hypothesized that a link between a genetic polymorphism in the serotonin transporter-linked promoter region (5-HTTLPR) of the *SLC6A4* gene which encodes for SERT may be associated with IBS. While individual studies gave conflicting conclusions, a recent meta-analysis based on a total of 27 studies including 7,039 subjects concluded that the SERT insertion/deletion polymorphism was associated with IBS in both Asians and Caucasians but only for those with constipation predominant IBS (IBS-C) (14). While other studies have variably examined the roles of polymorphisms

in genes encoding for other serotonin receptors, interleukin 10 (IL-10; an anti-inflammatory cytokine), alpha-2 adrenergic receptors, G-proteins and the cholecystokinin receptor and identified several polymorphisms within these genes which appeared to be associated with sporadic IBS, small sample sizes and lack of reproducibility in large data sets, together with the variability of the clinical phenotype, have engendered a cautious approach to the interpretation of these findings.

The somewhat unique nature of post-infection IBS (PI-IBS) has already been alluded to. Its recognition spurred interest in the potential role of the microbiota and the host immune response in IBS and, indeed, a study of one of the largest and best characterized outbreaks of PI-IBS identified a possible genetic predisposition to this syndrome (15). The municipal water supply of Walkerton, a small rural town in Ontario, Canada, located 180 km northwest of Toronto, was contaminated with *E. Coli* 0157:H7, *Campylobacter jejuni* and other pathogens in May 2000. Over 2,300 residents were affected by a resulting outbreak of acute bacterial gastroenteritis; there were 27 cases of haemolytic-uremic syndrome and 7 deaths. The Walkerton Health study followed the long-term health outcomes of this well-defined study cohort; three years after the outbreak, 36.2% of exposed residents fulfilled Rome I criteria for diagnosis of IBS (15). Three gene regions of interest, Toll-like receptor 9 (TLR9), IL-6 and cadherin 1 (CDH1), were identified; variants within these regions proved to be independent risk factors for the development of PI-IBS even when previously identified clinical risk factors were controlled for. In PI-IBS, at least, variations in genes involved in the host response (TLR9 and IL-6) and the gut barrier (CDH1) seem to predispose to the development of IBS. Could these findings extend to IBS in general? One study in a relatively small cohort containing individuals with sporadic IBS suggested that they did not (16); clearly this needs to be re-examined in a much larger cohort.

Genome-wide association studies (GWAS) have proven to be an important resource in defining the genetic architecture of many common diseases including Crohn's disease and ulcerative colitis. However, the limitations discussed in relation to attempting to correlate IBS with candidate gene polymorphisms apply to an even greater extent in a genome wide association study; very large cohorts of patients with well-defined phenotypes are required. For these reasons, the recent study from Bonfiglio and colleagues represents a real advance (17).

Their primary analysis was based on the UK Biobank and included 9,576 IBS cases and 336,499 controls; the study was, therefore, powered to detect modest genetic risk effects (17). Findings were then further assessed in a multi-national population of IBS patients attending tertiary referral centers and in a Swedish population cohort. Their GWAS analysis identified signals of suggestive significance in 14 independent loci including one genome-wide locus on chromosome 3q31.2 (rs10512344). This association held true only for females and, in the validation cohorts, was linked to constipation-predominant IBS. They went on to show that the IBS gene risk pool was significantly enriched for intracellular calcium activated chloride channel activity, ion gated channel activity and anion channel activity. Interestingly, in view of current interest in the role of micro-RNAs (miRs) in IBS, the IBS gene risk pool was also enriched in targets of miRs from the miR-15 family. This is of particular interest as members of the miR-15 family have been implicated in the regulation of gut barrier function and, via serotonin receptors, on motility (18,19). In one such study, another international consortium identified a single nucleotide polymorphism (SNP) within the 5-HT_4 receptor gene *HTR_4* in a small number of patients with diarrhea-predominant IBS (19). Interestingly, this SNP involves a binding site for the miR-16 family and miR-103/miR-107. In further studies, they demonstrated co-localization of the miR-16 and *HTR_4* genes in the colon supporting a role for miR16 in the regulation of this serotonergic receptor. As these miR's appear to down regulate the 5-HT_4 receptor whose main function is to promote motility, it should come as no surprise that levels of miR-16 and miR-103/miR-107 inversely correlated with bowel frequency and consistency. These results indicate that specific miRNA's and not just the 5-HT4 receptor itself could be targets for future drug discovery in IBS (19).

These associations between IBS and genes involved in the regulation of ion channels have been replicated in a GWAS meta-analysis from 5 independent European cohorts (20) and have also been demonstrated in studies employing candidate gene approaches (21).

These are exciting findings and provide, not only a real genetic basis for IBS but also mechanistic insights linking genes to relevant functions. These variants are rare (less than 4% of the population) and will only explain a very small proportion of IBS subjects. Nevertheless, studies such as these and others (22-26) are slowly but surely identifying distinct genotypes within IBS. Even collectively they but scratch the surface in terms of the pathophysiology of IBS, in general. Here, nurture still looms large (27). This

may not discount a role for genetics in the majority of IBS sufferers; we look forward to studies examining in detail interactions between environment and genome as well as the epigenetic effects of environmental and psychosocial inputs. Progress in the identification of biomarkers, if not for all of IBS, then for IBS subgroups may, in the future, will help to overcome the problems posed by the heterogeneous nature of the clinical phenotype in IBS.

One gets the feeling that the long-awaited dawn of IBS genetics has finally arrived—there is a long day ahead.

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