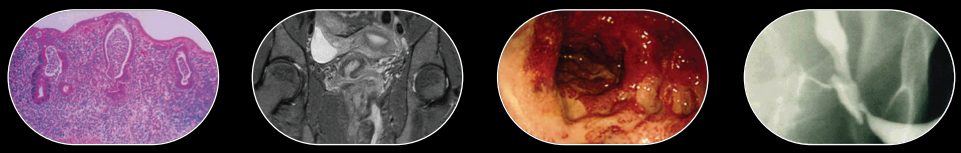

Clinical Dilemmas in

Inflammatory Bowel Disease

New Challenges

Second Edition

Edited by Peter Irving, Corey Siegel, David Rampton and Fergus Shanahan

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Preface

In 2006, three of us published a short book containing about 60 pithy and sometimes provocative chapters on controversial topics in IBD. These were selected with the aim of covering areas that commonly cause clinicians difficulties in decision-making. The book was well received but because of its subject matter has inevitably, at least in some chapters, become a bit out of date. Therefore, we have now produced a new book guided by the same principles as the first. A few of the chapters in this book are updates of their predecessors, but most are entirely new, reflecting the changing challenges faced by gastroenterologists at the beginning of the millennium's second decade. Our authors are almost all acknowledged experts in their fields and work wherever IBD is common in the world. To help widen the appeal of the book, for this edition we have engaged both a US coeditor (CS) and more US-based contributors than previously.

As before, we have deliberately chosen some tricky topics, and should point out that as editors we do not necessarily agree with all that is written here; if we did the book might be dull. Again, we hope the book will appeal both to senior and trainee gastroenterologists, as well as other members of the IBD team, and that readers will find that it provides a useful distillation and analysis of a wide range of current management dilemmas.

We are very grateful to all our coauthors, almost all of whom delivered their chapters on time and with minimal hassling. We are particularly grateful too to the team at Blackwell's, especially Oliver Walter for his support for the project and Jennifer Seward for her editorial work.

PMI, CS, DSR, FS July 2011

PART I:
Genes and Phenotype in IBD

1 Which will take us further in IBD—study of coding variation or epigenetics?

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LEARNING POINTS

- Genome-wide association scans have revealed many genetic risk factors for Crohn's disease and ulcerative colitis.
- As with environmental risk factors, some of the genetic risk is shared and some is specific to either Crohn's disease or ulcerative colitis.
- Only about 20% of the variance in heritability has been accounted for by known genetic loci.
- The study of genetic variants is valuable because it reveals insights into disease pathogenesis.
- Increasing evidence suggests that much of the host susceptibility to IBD may be epigenetic, lying at the level of the regulation of gene expression.
- Epigenetic risk is heritable through mitosis and possibly meiosis, and many of the known environmental or lifestyle risk factors may operate at an epigenetic level by influencing gene transcription.

Genetic susceptibility to inflammatory bowel disease (IBD) is complex. While genome-wide association scans (GWAS) have pushed Crohn's disease (CD) to the front of the field of complex disease genetics, the recognition that only 20% of the variance in heritability has so far been accounted for provides a salutary reminder of the challenges ahead [1]. The main achievement of GWAS has been to highlight a number of previously unsuspected pathogenic pathways for IBD and to provide a stable base-camp from which to explore the genetic higher ground—defining causal variants at each of the loci identified, accounting for the remaining 80% of heritability and exploring functional implications.

This chapter discusses what is understood regarding causal mechanisms in IBD genetics, particularly the relative contributions of simple variation in DNA coding sequence and epigenetic regulation of gene transcription. For some readers, epigenetic regulation of gene transcription may be an unfamiliar concept: it involves changes in gene expression resulting from mechanisms such as chromatin packaging, histone acetylation (affecting electrostatic charge and hence DNA binding), and DNA methylation.

Gene expression: sequence variation versus epigenetic factors

The human genome is thought to encode some 23,000 protein-coding genes, comprising just 1.5% of the total of 3 billion base pairs. Sequence variation can take many forms from single nucleotide polymorphisms (SNPs) to indels (insertion–deletion polymorphisms) to copy number variants, where segments up to thousands of base pairs long can be deleted or duplicated. SNPs are the commonest variant. They occur approximately every 200 base pairs, but less frequently in coding sequence because of potential for adversely affecting protein function and hence incurring negative selection pressure.

Genes comprise exons (the coding sequence) and introns, which are removed prior to mRNA being translated to protein. Gene density varies considerably, with lengthy tracts of noncoding sequence, formerly and erroneously

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referred to as "junk DNA," being interposed. Increasingly, it is recognized that much of the complexity of human biology derives not from the coding sequence, but from the complex, networked regulation of gene transcription by a host of epigenetic mechanisms. These include alternative exon splicing and control of mRNA stability by microRNAs, as well as DNA methylation and histone binding. These mechanisms (reviewed in [2]) allow dynamic activation or silencing of genes, and are heritable in being transmissible at mitosis, for example, to maintain tissue-specificity of gene expression, but they are not related to changes in DNA sequence.

Genetic variation in IBD

What forms of genetic variation contribute to IBD? The answer is likely to be "all of them," to a greater or lesser extent, perhaps including mechanisms yet to be characterized. Extrapolation from monogenic disease initially suggested that coding variation was likely to be most relevant, and its obvious impact on protein structure and function supported this intuition. Further, the three relatively common causal variants in NOD2, the first IBD gene to be identified, were all coding variants [3]. Thus, early genome-wide genotyping arrays, which could accommodate relatively few SNPs, focussed only on "nonsynonymous" SNPs. Although some interesting results were obtained, particularly in identifying the importance of ATG16L1 and autophagy in CD, the yield was unimpressive [4].

Truly hypothesis-free GWAS studies have followed, interrogating most if not all common variations (allele frequency >5%) genome-wide. Interestingly, the yield from these "proper" GWAS studies has been much greater than from nonsynonymous SNP scans and many lessons have been learned.

One remarkably consistent feature of GWAS studies has been the number of "gene deserts" showing association across a range of complex diseases. The supposition is that these loci contain elements that regulate transcription, and there is now evidence that sequence variation influences transcription for many genes. Thus, epigenetic regulation is itself a heritable trait and may be the key factor contributing to phenotypic variation in humans [5].

Several "gene desert" associations have been seen in IBD: indeed in the first meta-analysis plus replication of CD GWAS studies from the international IBD genetics consortium, 6 out of the 32 confirmed loci mapped to gene deserts. More than this, our now detailed knowledge of all common sequence variations genome-wide allowed us to identify how many of the CD susceptibility loci correlated with *any* known coding variation. The answer, rather startlingly, was just 9 [1]. To emphasize this point, coding variation has to date been confirmed as causal for just two loci—NOD2 and ATG16L1, with one other at IL23R strongly implicated.

Regulation of gene expression in IBD

Accepting the indirect evidence that regulatory effects are important, is there any direct evidence? The answer is emphatically yes. In the Belgian CD GWAS, the strongest association was seen with a 1.25-Mb gene desert on chromosome 5. Using publicly available expression quantitative trait loci (eQTL) data, Libioulle et al. showed that these same SNPs that showed association with CD also correlated strongly with expression of the prostaglandin receptor gene EP4 270 Kb away [6]. The international CD meta-analysis study identified a number of other such correlations [1], and in its most recent analysis identified association at a DNA methyltransferase gene, emphasizing the importance of epigenetic regulation and its interrelationship with sequence variation in CD susceptibility.

Evidence from basic research corroborates the importance and potential complexity of epigenetic effects. Thus, the toll-like receptor-induced inflammatory response in mouse macrophages is regulated at a gene-specific level by transient chromatin modification, with Th2 "bias" being conferred by a transcriptional regulator of IL-4 called Mina. Highlighting the interplay of sequence variation with epigenetics, production of Mina is itself strongly correlated with SNP haplotypes in its promoter [7].

Identifying correlation between IBD association signals and gene expression hints at functional regulatory elements, but usually does not explain the mechanism. The expectation is that genome-wide assays for DNA methylation, ChIP seq, histone binding, and DNA tertiary structure (e.g., chromatin conformation capture or 3C), will provide some answers over the next few years [8]. They should allow both a better understanding of the mechanisms underlying current GWAS signals and also permit de novo genome-wide studies.

Limitations of current studies of epigenetic mechanisms in IBD

At present, difficulties in defining which cell type to target for expression analyses are limiting. The relevance of this comes from the recognition that many gene regulatory effects are cell-type specific—as seen for the CD-associated allele of IRGM which affects expression in opposite directions in different cell types [9]. Further concerns relate to the confounding effects of inflammation and drug therapy. Nonetheless, the evidence that epigenetic mechanisms are crucial in regulating gene transcription and thereby affecting susceptibility to disease will drive development of the appropriate resources to tackle these questions.

Epigenetic regulation is also significantly influenced by environmental factors, including diet, smoking, and infection—all of which are implicated in IBD pathogenesis. For example, aryl hydrocarbon receptor (AhR) agonists, which are present in substances as varied as cigarette smoke and *Brassica* vegetables, can strongly influence COX-2 expression. The effect may be related to AhR acting directly as a transcriptional regulator and also by regulating histone acetylation and hence chromatin structure [10]. The AhR also plays a key role in modulating Th17 lymphocyte development through epigenetic mechanisms [11]. The suggestion that some epigenetic regulatory influences may be transmissible through meiosis to the next generation adds particular interest to this story [12].

Conclusions

At present, GWAS studies are being widely deployed not because they provide all the answers, but rather because they are technologically tractable and provide robust and reproducible data. More technologically challenging and complex studies will follow to advance our knowledge of the epigenetic regulation of gene transcription and its contribution to inflammatory disease [13].

The suspicion is that many of the pathways highlighted by GWAS studies will also be flagged as important for IBD pathogenesis by other techniques. A case in point might come from the confirmed association of noncoding SNPs adjacent to IL-10 with IBD [14], plus the recent observation that IL-10 gene expression in antigen-presenting cells is strongly regulated by the histone deacetylase HDAC11 [15]. Perhaps these findings are directly correlated, or maybe the GWAS signal is flagging a pathway influenced by many epigenetic and other mechanisms that themselves regulate IL-10 transcription and thereby influence IBD susceptibility.

All of these studies represent work in progress, and despite recent exciting developments this remains a field in its infancy. Nonetheless, current evidence suggests that for most individuals with IBD, coding variation is likely to have made only a modest contribution to their disease risk, while epigenetic regulation of gene transcription, perhaps influenced by environmental factors such as smoking, bacteria, and diet, play a much more important role.

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2 IBD in different ethnic groups: same or different?

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LEARNING POINTS

- There are many genotypic but few phenotypic differences in IBD in different ethnic groups.
- In relation to genotypic differences:
  - the NOD2 and IL23R gene polymorphisms highly linked to Crohn's disease (CD) in Caucasians appear to be absent in Asians;
  - few genes show homologous risk susceptibility in Asians and Caucasians: these include the tumor necrosis factor superfamily 15 (TNFSF15) gene for CD and the HLA region for ulcerative colitis;
  - among genes known to confer risk of IBD, there may be unidentified polymorphisms in Asians.
- The few phenotypic differences in different ethnic groups include a male preponderance of IBD in Asians and primary sclerosing cholangitis being rare in Asians.

Introduction

Inflammatory bowel disease (IBD) occurs worldwide but predominates in Western countries. However, in recent years there has been a marked rise in the incidence of IBD in developing countries, especially in Asia from where most non-Western IBD data are derived. Whether IBD in different ethnicities is the same disease is not certain. Disease similarities may be studied according to a comparison of their genotypes and phenotypes and help confirm analogous pathogeneses, natural histories, and responses to treatment. Comparing diseases may validate the generalization of IBD research and clinical practice across different populations.

Genotype

IBDs are polygenic diseases of variable penetrance that require a complex interaction with the environment and the intestinal microflora for phenotypic manifestation. Familial clustering of IBD differs in the West (up to 40% [1]) and Asia (0–7% [2]), but there are few data on twins, IBD concordance, and phenotypic concordance in low-prevalence ethnicities.

While there has been a vast increase in research in IBD genetics, especially using genome-wide association scans in Western populations, similar large-scale studies need to be replicated in non-Western populations. Data from Asian populations have been derived mainly from tertiary institutions as case-control samples, often through single nucleotide polymorphism (SNP) testing. What research has been done has highlighted differences in the genetic makeup of IBD in different ethnic populations, and while an extensive review of this area is beyond the scope of this chapter, NOD2 and IL-23R are used as examples.

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FIGURE 2.1 The percentage allelic frequencies of the 1007fs frameshift (SNP13) polymorphism of the NOD2 gene in Crohn's disease (CD) and controls from different countries, with author and year of publication.

The NOD2 Gene

Approximately 30% of patients of European ancestry have at least one of three SNPs linked to the development of CD. In contrast, the prevalence of NOD2 mutations in Asian IBD and non-IBD conditions is negligible at around 0% in the Chinese, Japanese, and Korean populations [4], although gene-sequencing studies have occasionally revealed rare novel NOD2 mutations of uncertain significance in Asians. While SNP8, SNP12, and SNP13 have been most closely linked to CD in Caucasians, SNP5 has been linked to the development of both UC (odd ratio (OR) 1.72, 95% confidence interval (CI) 1.17–2.52) and CD in India [5]. Figure 2.1 demonstrates the heterogeneity of the allelic frequencies of the 1007fs frameshift gene (SNP13) polymorphism in CD and controls from different countries.

The Interleukin 23 Receptor

The interleukin 23 receptor (IL-23R) and Th17 pathway mediates microbial defense and intestinal inflammation [6]. Multiple genes along the IL-23 signaling pathway are associated with both CD and UC. The Arg381Gln SNP of the IL-23R on chromosome 1p31 was found to protect against the development of CD in Caucasians

[7]. However, in the Japanese population there was no association with CD in a study of ten IL-23R SNPs in 484 CD patients and 439 controls [8]. The same study also found that some SNPs that are found in Caucasians are entirely absent in the Japanese population, further demonstrating the genetic divergence between different ethnicities. Using DNA direct sequencing on a Chinese cohort, T allele carriers at the rs11465788 marker of the nontranscribed intron were significantly lower in 134 CD patients (75%) compared with 131 controls (91%, $P < 0.0005$) [9]. As the DNA intron region does not code amino acids, epigenetic factors may influence IBD pathogenesis (see Chapter 1). The CD phenotype of this polymorphism (nonstricturing, nonpenetrating) did not match that of CD Caucasian patients (ileal, stricturing), and a larger replication study needs to be performed. However, the study suggests that different gene polymorphisms affecting similar pathogenic pathways may occur in different racial populations.

Phenotype

IBD phenotypes differ between and within populations, and there are no distinguishing phenotypes that separate Western from Asian IBD. Male predominance of CD is a common feature of IBD in developing countries, but smoking may be a confounding factor [10]. CD and UC behavior and extent appear similar in Asian and Western IBD. Despite the genotypic differences between Western and Asian IBD, the lack of phenotypic differences supports the concept that IBD is a heterogenous collection of diseases that are not race-specific. These findings, plus the rapid increase in disease incidence, suggest that environmental factors also play a crucial role in the development of IBD.

Age

The age of diagnosis of CD in Asia is similar to, or older than that of Western countries. A younger age of diagnosis of CD in Asia is associated with a worse prognosis, with greater number of flares and requirement for azathioprine. In Caucasians, a younger age of diagnosis of CD is also associated with a worse outcome with earlier stricturing and penetrating complications and requirement for surgery.

In a cohort of Chinese UC patients from Hong Kong, the median age at diagnosis was 37 years (range 12–85) with an equal distribution of men (52%) and women [11]. In comparison a review of studies of North American populations found a slight predominance of females (48–65%) and that age of diagnosis ranged from 33 to 39 years [12].

Behavior

The behavior of CD in Asia resembles that in Western countries. Despite the negligible contribution of the NOD2 SNPs in Asian CD, terminal ileal stricturing disease is still apparent but in lower proportions than Western CD, suggesting that these gene polymorphisms are not necessary for the development of tCD features.

The evolution of CD behavior with time leads to a progressive increase in patients developing stricturing or penetrating phenotypes in both Western and Chinese populations [13].

Location

The location of CD remains relatively stable over time in both Asians and Caucasians. In one cohort of Chinese CD patients, 19% of patients had gastrointestinal involvement proximal to the terminal ileum . However, isolated small bowel disease is uncommon in Chinese patients (4%) in comparison with Western patients (24–45%); Table 2.1 compares the location of CD in the Hong Kong Chinese with Western series. For UC, the extent of inflammation in Asia is similar to Western studies when similar patient recruitment methodologies are employed [18,19].

TABLE 2.1 A comparison of the locations of Crohn's disease (CD) in percent in different countries based on the Vienna classification

Crohn's disease (CD) location	Hong Kong [4]	Stockholm Sweden [14]	Perth Australia [15]	Vancouver Canada	Liege Belgium [16]	New York USA [17]
Terminal ileum	4	28	24	25	45	26
Colon	30	52	42	27	27	39
Ileocolon	44	14	34	35	24	22
Upper gastrointestinal tract	19	6	0	13	4	12

Dysplasia in UC

A recent multicenter study from Korea revealed a high cumulative rate of colorectal cancer (CRC) in UC patients over time [20]. The cumulative risk of UC-associated CRC was 0.7%, 7.9%, and 33.2% after 10, 20, and 30 years of disease, respectively. Whether the particularly high rate of CRC with long disease duration relates to differences in disease behavior or is a result of other factors, such as knowledge about and use of screening and chemoprevention or perhaps methodological issues with the study, is unclear.

Extraintestinal Manifestations

In general, the proportion of patients having extraintestinal manifestations (EIM) in Asia is similar to Western series with 6–35% of IBD patients having at least one EIM [16,21]. However, the incidence of primary sclerosing cholangitis is much lower in Asian IBD patients [22,23].

Conclusions

Geographic variance in IBD prevalence is related both to genotypic variations and environmental risk factors suppressing or promoting phenotypic expression. Recently, there has been an increase in the incidence of IBD in many parts of the world, the phenotype occurring being remarkably similar to that of Western IBD populations in terms of disease location, severity, behavior, and complications. EIM and mucosal dysplasia in chronic colitis also occur. Overall, there are more differences in IBD phenotype within a race than between races. Therefore, similar IBD pathogenic pathways and responses to treatment could be expected in different ethnicities.

However, the genotype of Asian IBD differs markedly to that of Western IBD. The near absence of NOD2 and IL-23R gene polymorphisms in Asians may indicate alternative polymorphism locations that are currently not tested for on SNP studies. There is a need to perform high-quality genome-wide association (GWA) studies in non-Caucasian populations to confirm this. On the other hand, it is possible that a complex interaction between genes, cytokines, signaling molecules, and the gene epistasis means that mechanisms of intestinal inflammation that differ between ethnicities may result in common clinical manifestations.

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