Inflammatory bowel disease (IBD), an immune-mediated disease, includes Crohn’s disease (CD) and ulcerative colitis (UC). It is believed that IBD occurs as a combination of environmental exposures and alterations in the intestinal microbiome that, in genetically susceptible individuals, leads to dysregulated aberrant immune activation. Genome-wide association studies have become commonplace in the last decade and have in turn elucidated many new IBD risk loci facilitating our understanding of relevant biological pathways. To date, IBD has the largest number of susceptibility variants identified among various autoimmune diseases. Despite these advances, it remains unclear what functional role these genetic variants play in disease phenotype and response to therapy; new knowledge of these biological pathways is already helping to develop novel targets for future treatment. Overall, the outlook for better treatment and prevention remain top priorities for the research community seeking to incorporate the latest genetic findings into the IBD puzzle.
have been discovered and new associated pathways described; these new associations in time will help us understand the mechanisms involved in disease development and aid in developing future targets for therapy. New biologic targets are of extreme importance since existing therapies are not consistently effective in all patients and nearly 1/3 of our patients lose their response to existing therapies over time. In addition, a better understanding of disease etiology, inherited mutations, and aberrant pathways will help to develop reliable biomarkers that are useful in identifying patients at risk for more aggressive disease in earlier stages and may also serve to direct a more personalized and effective treatment regimen.

The History of Genetics in IBD

The combination of high-throughput genotyping, which enabled genome-wide association studies (GWAS), and next-generation sequencing technologies have led to the identification of numerous risk variants in IBD. The first evidence that IBD had a heritable component stemmed from familial aggregation and concordance studies among monozygotic and dizygotic twins. These studies provided heritability estimates of IBD and its overlap in development of both UC and CD. Nearly a decade ago, the first and strongest IBD genetic risk factor in NOD2 (nucleotide-binding oligomerization domain-2) was identified through refined approaches including genetic linkage studies and candidate gene analysis. Thereafter, multiple IBD risk loci have been identified through GWAS approaches and the meta-analyses that followed.

Basic GWAS uncovered IBD risk loci by comparing the frequency of thousands to millions of individual genetic variants found in a cohort of IBD patients to those of “healthy controls” (individuals without IBD). The frequency of a particular allele at a genetic variant may differ between IBD patients and controls and thereby show association to IBD susceptibility. The most recent landmark study representing one of the largest genetic association efforts performed for any chronic disease encompassed 15 different genome-wide association studies and included information on >75,000 IBD patients and controls examining 1.23 million genetic variants. In this meta-analysis, a total of 163 IBD-related susceptibility loci were identified, of which 71 were reported for the first time. An unexpected overlap between UC and CD was observed, with 110 of the 163 loci shared by both diseases. These 163 variants now explain ~14% of the disease variance in CD and ~8% in UC, indicating that there are many more genetic factors yet to be uncovered to account for the entire genetic component of IBD.

What Have We Learned About IBD Genes From GWAS?

Most practicing gastroenterologists deal with the intricacies of IBD patients and the ever-growing complexity of treatment regimens. In the same fashion, genetics in IBD parallels complex clinical scenarios. IBD does not follow simple Mendelian genetic patterns resulting from single genetic mutations predisposing to rare diseases (e.g., cystic fibrosis). It is important to recognize the subtle difference between the use of terms like “mutation” and “variation or polymorphism”. The use of “mutation” often refers to a genetic change that is rare and abnormal in the general population and that in the context of disease, can be causative. Alternatively, “variation” or “polymorphism” as in single-nucleotide polymorphisms (SNPs) are genetic changes that are common in the population such that alternative forms of the genetic code at that position in the genome is in itself insufficient to cause disease. Therefore, even when inherited genetic risk variants are found (e.g., via GWAS) to be attributed to increased risk/susceptibility of IBD in large population studies, it remains difficult to predict disease development at the individual patient level since the degree of penetrance of these genetic changes is highly variable. The simple inheritance of any of the currently known genetic risk variant is insufficient by itself to cause disease.

The currently identified IBD loci are almost exclusively associated with “risk” of disease; however the exact biological mechanism underlying this association is often not clear. By the nature of their design, GWAS often examine common (>1%) variation; these genotyping arrays do not typically survey the role of rare (<1%) genetic variants, which it is believed may explain a considerable proportion of the so-called “missing” heritability. For instance, if we consider only the most associated SNP within NOD2, we only account for 0.8% of genetic variance; by examining all three NOD2 coding mutations (some rarer in frequency), we can account for nearly 5% of the genetic variance of CD. If the same were true of the 163 risk loci, they could explain a more significant proportion of the overall heritability. Future work in genetics may lie 

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in identifying further genetic variability within known IBD risk loci. Furthermore, once identified, the focus must shift to understanding the functional effects of these variants on IBD outcomes.

An interesting and unexpected finding learned from IBD GWAS studies is the substantial genetic overlap observed between IBD and immune-mediated diseases. Seventy percent (113/163) of the IBD loci are shared with other complex diseases. IBD-associated diseases include rheumatoid arthritis, type 1 diabetes, celiac disease, multiple sclerosis, and systemic lupus erythematosus. The strongest enrichment in genetic overlap is currently seen with ankylosing spondylitis and psoriasis. This overlap is driven by genes involved in immune cell signaling, T-cell differentiation and innate immune responses. While these genetic regions of disease overlap have been examined independently by a number of investigators (including the ImmunoChip Consortium), a large cross-disease effort is currently underway to understand the immunological pathways and to elucidate the mechanistic role of these genes in each of these diseases. The end result will hopefully provide a better understanding between the immune pathways and disease outcomes in IBD.

Lastly, IBD-associated variants are enriched in genes coding for primary immunodeficiencies and susceptibilities to mycobacterial infections. The implicated genes correlate with reduced levels of T-cells, Th17, memory or regulatory T-cells. Similarly, six of eight known autosomal genes for Mendelian susceptibility to mycobacterial infections are associated with IBD risk. Similar results are seen in GWAS of both leprosy and primary immune deficiencies associated with skin infections such as staphylococcus and candidiasis. These associations highlight that another barrier function.

Can We Predict Disease Behavior from Our Current Knowledge of IBD Genes?

As it currently stands, we are not at the stage where we can apply IBD genetic susceptibility to clinical practice. A primary goal of “genomic medicine” is to directly apply our findings into clinical decision-making. Prediction of disease phenotype and response to therapy are two main areas in which genomics become directly applicable. IBD genetics may aid in predicting disease phenotypes, including disease location, behavior, and extra-intestinal manifestations.

The most consistently replicated association is that between NOD2 and ileal fibrostenosing CD. Approximately 46% of patients with fibrostenosing ileal CD carry at least one rare disease-associated allele at NOD2 compared to 24% of those without this phenotype. Additional allelic associations with ileal CD include ATG16L1 and TCF7L2 genes involved in autophagy and the Wnt transcription factor, respectively. A recent study by Cleynen et al identified that patients with NOD2 mutations also had a threefold higher risk for complicated CD including surgical resections. The identification of these genotype/phenotype associations may help guide earlier aggressive management in affected patients. Similar studies attempt to arrive at clinical conclusions by grouping known variants together. A recent Dutch study of CD patients found that an increase in the number of CD risk alleles (across NOD2, IBD5 locus, DLG5, ATG16L1, and IL23R) was associated with an increased risk of CD complications. Similarly, a group in Spain calculated an individual’s genetic risk score based on significantly associated variants. They found patients with a higher risk score were more likely to develop a complicated course of disease.

Can We Use Genetics To Predict and Assess Response to Therapy?

Yes, but only with the use of immunomodulators. Genetic prediction models for response to anti-TNFs are still under investigation. The widest use of genetics in IBD treatment is thiopurine methyl transferase (TPMT) genotyping and enzyme activity to guide response and to predict adverse effects. A low TPMT enzyme activity shunts 6-MP metabolism towards increased production of 6-thioguanine nucleotides (6-TG), putting patients at increased risk for leukopenia. A recent review identified that the sensitivity of specific TMPT genotypes in determining enzyme activity was 80%. Even the genotyping of the four most common variant alleles within this enzyme does not correlate absolutely with enzyme activity. The use of genotyping is also limited by recent blood transfusions. Although genetic testing of TPMT, prior to the initiation of thiopurine treatment, is a cost-effective, it has limited utility in predicting response to therapy.

Studies of a genetic variant that can predict
response to anti-TNFs have yielded inconsistent results. Previous studies have shown positive results when examining variants in TNF-α and TNF-α receptors for their predictive ability to respond to infliximab in CD patients. However, follow-up studies failed to replicate these findings.21-24 Arijs et al. surveyed infliximab-naïve UC patients, examining gene expression patterns using microarray technology, and found that IL23α2 expression levels were predictive of responders and nonresponders with 100% sensitivity and 91% specificity.25 Hlavaty et al., genotyped 287 patients with refractory or fistulizing CD for 21 apoptosis-related genes and found that variants in the FasL/Fas system and caspase-9 influenced response to infliximab.26

Although the current genetic approaches are accessible at a near cost-effective level, applying this information directly into clinical practice remains problematic. Several studies have developed prediction models using identified IBD associated genes with several additional biomarkers.17, 27, 28 Yet, such genetic predictors of disease behavior and therapy have limited prognostic ability, limiting their current clinical utility.29

It’s Not Just About Genetics

IBD pathogenesis, like many other complex immune disease phenotypes, is believed to be the result of environmental exposures in genetically susceptible hosts. Not everyone that carries the risk alleles at the established IBD loci will develop disease. The rising incidence of disease in industrialized nations suggests a rather strong environmental component as more people are exposed to a Western-type lifestyle, including diets high in fat and carbohydrates.30 Studies of changes in dietary intake can lead to alterations in the GI microbiota, increasing pathobionts (situational pathogens).31 In genetically susceptible hosts, changes in the microbiome may be the key that triggers aberrant immune pathways and the development of IBD.

CONCLUSION

IBD pathogenesis involves the combination of multiple risk factors, the search for which is overwhelming. In the future, customized genetic assays designed specifically to interrogate the expanding catalogue of IBD relevant genetic variation will be able to inform disease treatment. Genomic profiles, inclusive of pharmacogenomic data and sensitive biomarker analyses, will have a significant influence on IBD treatments, drug monitoring, disease management, and perhaps even disease prevention or elimination. Undoubtedly, the future in personalized IBD medicine will be in tailoring treatment regimens to both our genome and microbiome.

References