

Finding inflammatory bowel disease genes will lead to a cure

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The opinion that finding inflammatory bowel disease (IBD) genes will lead to a cure is based on the fact that genetic variation provides a vast reservoir of information specific to individual patients that is only beginning to be acknowledged on a large scale. Complementary to this is that, in many respects, IBD represents an ideal genetic disorder(s). First, the significant role of genetics in IBD is firmly established based on the significant familial clustering observed, combined with significantly higher concordance of monozygotic twins compared with dizygotic twins (1). The diagnostic pathogenic certainty associated with the diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) is high; heterogeneity probably exists in clinically similar cases but is likely relatively limited. Compared with other multigenic disorders, the relevant tissues – the peripheral blood leukocytes and the intestinal tissues – are easy to obtain for expression studies. There are numerous, excellent animal models that exist in IBD (2) for which several lines of evidence provide correlative support in humans. The fact that at least two well-replicated disease associations exist in IBD – nucleotide oligomerization domain 2/caspase activation and recruitment domain 15 (*NOD2/CARD15*) (3,4) and *IBD5* on chromosome 5q (5,6) – holds out the promise that the increased understanding of disease pathophysiology will accrue from genetic approaches.

At least three mechanisms can be defined through which genetics can effect cures for IBD. First, if effective, preventive approaches can be developed, feasibly powered studies will require the identification and prospective follow-up of high-risk individuals which will be best achieved through testing of established IBD genes. Second, the identification of genuine IBD risk alleles will often provide very novel insights into the mechanisms of disease pathogenesis that fundamentally change existing paradigms of disease pathogenesis. Finally, genetic approaches refine the understanding of key pathways that lead to human IBD.

PREVENTING DISEASE: IDENTIFICATION OF THE HIGHEST RISK INDIVIDUALS

The prevalence of IBD is too low in the general population to anticipate that effective, preventive interventions can be developed on a population-wide basis. Rather, prospective, preventive and epidemiological studies will need to be applied within currently unaffected relatives of IBD probands. These highest risk individuals include monozygotic twins, children of parents who are both affected by IBD, and *NOD2/CARD15* homozygous and compound heterozygous relatives of CD probands. In a large trio-based cohort (7) (affected child plus both parents studied), 145 of 1952 (7.4%) parents of CD children had the disease. Of 69 parents homozygous for the *NOD2/CARD15* mutations,

16 (23.2% risk of CD) had CD (the estimated risk of developing CD given *NOD2/CARD15* homozygosity only applies to relatives of CD patients). It was predicted that the risk of siblings of CD probands developing CD would be at least comparable to that observed in parents, given the more similar developmental and environmental factors shared by siblings compared with parent-child pairs.

GENETICS PROVIDES NOVEL INSIGHT INTO MECHANISMS OF DISEASE PATHOGENESIS

The identification of *NOD2/CARD15* mutations and their association to CD has resulted in fundamentally different ways of thinking about CD and host-bacterial interactions. It has resulted in a more balanced view by the community at large on the relative importance of the innate arm of the immune system. It has highlighted the importance of intracellular microbial sensing mechanisms, as well as the potential role of alpha-defensins in intestinal immune homeostasis (8-10). Finally, the identification of relatively uncommon amino acid polymorphisms in innate immune receptors provides an important new class of genetic variants that defines interindividual variability in host-environment interactions (11).

A new genetics approach that is increasingly being applied to multigenic disorders is the application of genome-wide association studies (12,13). The underlying premise for this approach is that most IBD risk alleles are relatively common in the population (common disease, common variant hypothesis). If multiple functional polymorphisms, each exerting subtle functional effects, are simultaneously required for disease development to achieve the expected population prevalence, each of these risk alleles must be relatively common in the control population. It is estimated that seven million single nucleotide polymorphisms (SNPs) with a minor allele frequency of at least 5% exist. Because many of these SNPs are in linkage disequilibrium with each other (ie, they 'travel together'), only several 100,000 well-selected SNPs are required to sample much of the common genetic variation in the human genome. Current genetic technologies are presently available to test this magnitude of SNPs. It is anticipated that the testing of 1000 cases and controls each would be adequately powered to identify a significant fraction of contributing risk alleles. Challenges of completing and interpreting genome-wide association studies include pathophysiological heterogeneity, the need for extensive replication and the lack of current analytical framework for testing for locus-locus interactions. Obtaining this extraordinary amount of genetic information on a cohort of patients in whom extensive phenotypic information is available, including expression studies and the capacity to follow prospectively, represents an extremely promising mechanism of identifying important new connections

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among genotypes, disease course and effects on disease expression. As information on genetic patterns and functional polymorphisms accrue, and costs for dense genome-wide typing fall, it is likely that comprehensive genetic testing will be more universally used in genetic and translational studies, and ultimately, used in clinical practice.

GENETICS REFINES UNDERSTANDING OF KEY PATHWAY DEFINITIONS

Many of the crucial pathways that lead to human IBD may have already been identified through various animal models of IBD. A comprehensive understanding of IBD involves integrating information obtained from animal models, functional human polymorphisms and various expression studies from human tissues. One illustrative example (14) involves the *mdr1a* (-/-) knock-out model of IBD, which spontaneously develops colitis. Genetic variants within the *MDR1* gene or pathway that result in decreased expression or function are strong candidates for disease association. The *MDR1* gene is a member of the ATP-binding cassette of membrane transporters and is located within a region of suggestive linkage on chromosome 7q. Polymorphisms within the gene that affect gene expression and activity have been reported. Some positive studies of IBD association have been reported, but definitive replication has not occurred. However, the finding of decreased expression of *MDR1* in intestinal tissues from CD and UC provides strong

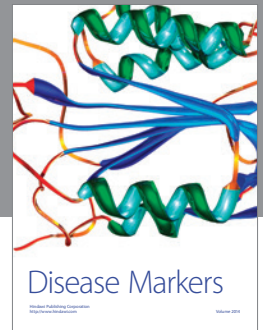
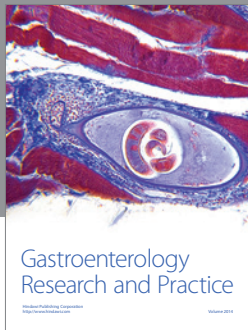
correlative support in human disease that the *MDR1* pathway is likely important, meriting therapeutic consideration (15). The *MDR1* promoter includes elements for beta-catenin and T cell factor (16), and the pregnane X and retinoic acid receptor (17) heterodimeric transcription factors. Recently, the association of a polymorphism to IBD genes in pregnane X receptors that affect expression of *MDR1* has been reported, which further highlights the importance of the *MDR1* pathway in IBD pathogenesis (18).

CONCLUSIONS

It is anticipated that in the not too distant future, the cost-effective means of comprehensively genotyping functional human polymorphisms and/or resequencing individual genomes will be available as a diagnostic tool for clinicians. This future diagnostic tool will provide a wealth of crucial information; the inherent complexity of interpreting this wealth of data should not deter us from starting this inevitable process of discovery. Education of current and future physicians in genetics will be an integral part of this process. The development of new IBD therapeutic algorithms would ideally involve a creative integration of therapeutic interventions with information on individual genetic backgrounds. The specific therapeutic challenges in IBD include its chronicity, intermittence and paramount need for safety. These challenges can best be met through individualized approaches and integrating knowledge of genetic factors.

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