

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Genetic Testing in IBD Patients

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G&H Can you briefly summarize the reasoning behind the hypothesis of a genetic component to inflammatory bowel disease?

DR Two historic observations have been made that have led to the assumption of a genetic component to inflammatory bowel disease (IBD). The first was the observation of families in which multiple members had IBD and that, within these families, the type of inflammatory disease, location in the bowel where it manifests, age at diagnosis, and sometimes even extraintestinal manifestations, were similar. In and of itself, this finding does not confirm a genetic association because if this were an environmental cause (eg, an infectious disease), one might anticipate a similar exposure among multiple family members as well.

However, the other historical observation providing a clue to the genetic component of IBD is that Ashkenazi Jewish individuals have a four- to five-fold increased risk of developing IBD than do non-Jewish whites. This suggests what is considered a population-genetics or ethnic-genetics influence in the disease. Subsequently, family studies, linkage analysis, and gene mapping have all confirmed an important genetic component to the disease.

G&H Are genetic factors the only variables in the development of IBD?

DR The current theory regarding the cause of IBD is that it is a condition in which a genetically susceptible individual is exposed to some environmental trigger or environmental factor that leads to a dysregulated immune system. As one might imagine with this model, the relative contributions of each of these features could vary greatly

from one individual to the next. One patient may have a stronger genetic component and require very little from the environment to trigger dysregulation. Another might have a very strong environmental component (eg, an infection or active cigarette smoking) that with a smaller genetic component would lead to disease presentation. In addition, there are a host of factors related to the gut and how it regulates its immune system that could lead to dysregulated immune function. So, for every individual with IBD, there is most likely some combination of these factors that lead to individual phenotypes within the spectrum of phenotypes we know as the different types of IBD.

G&H Is there a single gene that offers the most compelling evidence for a genetic component?

DR Yes. So far, the strongest genetic variant associated with IBD is the *NOD2/CARD15* gene, located on chromosome 16, which has been associated with patients who have Crohn's disease of the ileum. The *NOD2/CARD15* variants have now been found in many populations around the world, with the notable exceptions of Japan and South Korea, where the incidences of IBD are lower than in Western nations and *NOD2/CARD15* variants have not been seen.

G&H How is the discovery of the *NOD2/CARD15* gene being utilized in ongoing research?

DR There is considerable ongoing research regarding *NOD2/CARD15* and the function of its protein, which offers an explanation of the pathogenesis of Crohn's disease. The *NOD2/CARD15* protein has two functional domains, one of which is involved in the detection of bacterial peptidoglycans and the other of which is involved in cellular inflammatory signaling. There are actually three main variants of *NOD2/CARD15*, which account for about 81% of those patients and families who have been described in studies. Among those three variants, one in particular—an insertion variant located in the bacterial detection domain (3020ins)—appears to play the most significant role. Pediatric and adult studies have found this variant to be associated with stricturing ileal disease and an earlier need for surgery and the need for repeat

surgery. If validated, this information may be useful for clinicians. Other work continues to examine the concept of a gene-dose effect of *NOD2/CARD15* and assessment of the penetrance of mutations in this gene. Such information is critical in order to provide meaningful interpretation of the *NOD2/CARD15* variants for patients and unaffected individuals.

G&H Are other genes being examined or is current research limited to *NOD2*?

DR We know that IBD is not a simple genetic disorder in which a single gene alteration determines disease expression. It is a complex genetic disorder that likely involves multiple genes, variable disease expression (penetrance), and additional factors that modify or augment the gene expression. People with different genes may have the same phenotype of disease; alternatively, people with different phenotypes of disease expression may have the same genetic make-up. Other genes have been proposed (Table 1) and, though they have not had the same strength of association that has been seen with *NOD2/CARD15*, they appear to be associated with IBD. Ongoing work with larger sets of families and affected individuals is likely to identify additional important candidate genes, including the one (or ones) associated with the prevalence of IBD among Ashkenazi Jews.

G&H How are genetic tests generally utilized in clinical practice?

DR In order for a genetic test to be clinically useful, it must provide information that would alter our management strategy. Thus, a test that could provide definitive diagnostic information would be very useful. Tests that can provide prognostic information would allow physicians to choose more aggressive therapy in patients that have more severe disease. Tests might also predict a response to therapy, in which case physicians could choose therapies that are more likely to work in individual patients. Lastly, tests for disease susceptibility may facilitate the screening of at-risk populations and, if paired with effective disease-preventing interventions, might ultimately reduce the incidence of IBD.

G&H How close are researchers to achieving these goals in the treatment of IBD?

DR When it comes to IBD, none of these goals has been completely achieved. In regard to disease diagnosis, there are limited data showing that the *NOD2/CARD15* test, and certainly not other, less well-described markers, can aid in diagnosis. Only a small number of the total Crohn's population carries *NOD2/CARD15* mutations. In addition, the penetrance, or likelihood of the gene express-

Table 1. Genes Associated with IBD Currently Under Investigation

Marker	Possible Association
<i>NOD2/CARD15</i> , Chromosome 16	CD, associated with detection of bacterial peptidoglycans
<i>OCTN</i> (novel organic cation transporter), Chromosome 5	Interaction with <i>CARD15</i> mutations associated with CD and UC
<i>DLG5</i> (<i>Drosophila</i> Discs Large Homolog 5), Chromosome 10	Possible inflammatory signaling
HLA class II molecules	CD, Steroid-dependent and medically refractory UC (and therefore colectomy), Large- and small-joint IBD-related arthropathy
<i>TLR4</i> (toll-like receptor protein 4)	Impaired lipopolysaccharide signaling and increased susceptibility to Gram-negative infections

CD = Crohn's Disease; HLA = human leukocyte antigen; IBD = inflammatory bowel disease; UC = ulcerative colitis.

ing itself, may be as low as 5%. Therefore, at this time, reliable use of this genetic marker for disease diagnosis is not possible.

With regard to severity of disease, there has been a suggestion of genetic markers to predict refractory disease or likelihood of required surgery. As mentioned above, there is limited work to suggest that a single *NOD2/CARD15* variant predicts the need for surgery or repeat surgery, but this has not been prospectively verified and, at this time, would not change our management paradigm. In addition, limited work has described the role of the multidrug resistance (MDR) gene in Crohn's disease. The MDR gene was first described in leukemia patients who did not respond to chemotherapy and has since been correlated to Crohn's disease patients who do not respond to steroids. In IBD, these patients have been more likely to require additional therapies or surgery. However, this remains retrospective and is not useful enough to supplant our current treatment algorithms. Clinically, when patients are steroid-refractory, we know quickly and adjust therapy. A genetic marker is not required to make this decision.

There is also research ongoing in pharmacogenomics, which examines the genetic polymorphisms of enzymes that metabolize drugs, allowing the prediction of likelihood of response and safety of therapy. The best-described test, which has been thoroughly tested in pediatric populations for non-IBD diseases and is now being studied in the IBD population, is the *TPMT* polymorphism for 6-mercaptopurine and azathioprine (Imuran, Prometheus)

metabolism. A prospective trial is currently examining whether TPMT testing can change clinical outcomes or safety in patients with Crohn's disease. There have also been small studies conducted in Belgium examining a marker that predicts response to infliximab (Remicade, Centocor), a biologic therapy for Crohn's disease and ulcerative colitis. However, these findings require validation and confirmation in larger studies and additional patient populations.

In regard to disease susceptibility, there is no stronger predictor of IBD onset than family history. Although the idea of administering *NOD2* tests in unaffected family members is appealing, the reality is that these tests have not provided a reliable level of predictability thus far, and, importantly, we do not know what intervention to suggest in those who may be *NOD2/CARD15* mutation carriers. An obvious suggestion is that family members of IBD patients should not smoke tobacco, given its strong association with Crohn's disease. However, genetic testing of disease susceptibility is not required to make such a recommendation.

G&H Would physicians require training in order to utilize these tests?

DR When physicians do have access to a genetic test or tests (I suspect it might be a test panel that will ultimately be available), it will be critical that they understand how to inform patients of the results. In other tests, results have been misinterpreted and patients advised incorrectly. Most commonly, a negative test will lead to the idea that the patient is not at risk for the disease, when, in fact, these results are indeterminate. Without a marker (or markers) documented in an affected family member to confirm it as meaningful in association with the disease state, a negative test result cannot be considered definitive. These patients should not be told that they are not at risk. Advances in our understanding of the genetics of IBD will require widespread educational programs and efforts to assure appropriate choice of who to test and how to interpret the results. It is unlikely that genetic counselors will be available in sufficient number (or that funds for reimbursement will be available) to do this.

G&H Is there patient resistance to the idea of genetic testing?

DR Genetic information is often viewed by patients and healthcare providers in a unique way that makes it more difficult to offer without substantial education and protection. At the University of Chicago, we conducted focus groups with patients regarding their interest and concerns regarding genetics and IBD. As with other populations that have been studied, the patients and their unaffected

family members in our groups expressed a fear of genetic discrimination, specifically in health insurance, life insurance, and employment. They expressed these fears despite the fact that there have not been any documented cases of such discrimination occurring based solely on genetic susceptibility. These fears are based on the fact that people view their genetic information as intensely private, unchangeable, and as revealing information about not only themselves but also their families. This concept is widely known as "genetic exceptionalism," where patients think of genetics as somehow special, despite the fact that these simple blood tests are in some ways no different from undergoing a complete blood count. Future use of any genetic testing in the IBD population will need to address these concerns.

G&H Can you discuss the economic feasibility of genetic testing?

DR A genetic test must be affordable. If it's not affordable in comparison to standard measures, it will never be used. Furthermore, patients who are afraid of discrimination may decide to be tested only if they can pay out of pocket and avoid reporting the test to their insurer. Another issue, one that arises repeatedly in the setting of genetic testing for cancer, is the practice of testing on patients who already have a disease in order to understand potential risks to other family members. The test doesn't help the patient who is already diagnosed. It is being administered to help their children or brothers or sisters. In this light, whose insurer should pay for this test? The patient's or their family member's? All of these issues complicate the economics of genetic testing.

Suggested Reading

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