Genetic Breakthroughs in the Study of Crohn's Disease

In a landmark finding, researchers announced the discovery of the first gene that confers susceptibility to Crohn's disease, a debilitating form of inflammatory bowel disease affecting an estimated 500,000 Americans. A targeted, interdisciplinary collaboration among scientists from different fields revealed that a mutated form of a gene called *NOD2* significantly increases a person's risk for developing Crohn's disease. This discovery is built upon research into how genetic and environmental factors combine to initiate an aberrant immune response that cascades into a destructive inflammation of the digestive system.

Crohn's disease typically afflicts young people in their teens and twenties, although it can strike at any age—as President Dwight Eisenhower discovered in his 60's. Symptoms include intestinal inflammation, nutritional deficiencies, abdominal pain, diarrhea, and rectal bleeding. For decades, the only treatment was surgical removal of the affected regions of the intestine. While research has since made possible less drastic alternatives, including oral medication and nutritional supplements, the majority of Crohn's patients still require surgery even today.

A complex interplay of environmental and genetic factors cause Crohn's disease. The environmental component involves the benign bacteria that normally live in our intestines. In healthy people these bacteria do not incite an attack by the immune system, but the immune system of patients with Crohn's disease reacts abnormally against these innocuous bacteria, unleashing destructive inflammation. Evidence for a genetic component comes from research on families in which individuals have the disease. Crohn's disease appears to be genetically complex, involving two or more genes, thus making the hunt for genes involved especially challenging. Research into the genetic and environmental causes of Crohn's disease could lead to the design of novel therapies and new methods for identifying individuals at risk for developing the disease, facilitating early intervention.

Important clues about the genetic and environmental factors underlying Crohn's disease have emerged from studies in animals. In an innovative study, scientists identified a variety of genes in healthy mice that were turned on or off in response to the presence of normal intestinal bacteria. This new knowledge of the response of healthy gut tissue to harmless bacteria may help scientists understand how this response goes awry in Crohn's disease. For insights into the destructive immune response of Crohn's disease, scientists studied mice known as SAMP1/Yit mice, which are genetically predisposed to developing Crohn's-like intestinal inflammation. When these animals are housed in special "germ-free" conditions they remain disease-free, demonstrating that genetic factors alone will not produce the disease. However, in the presence of normal environmental bacteria, SAMP1/Yit mice develop intestinal inflammation that remarkably mimics that of human Crohn's disease. The inflammation in the mice appears to be mediated by immune system cells called "T cells." These cells produce a protein called TNF-α which promotes inflammation. This work also further validates the use of SAMP1/Yit mice as a model of Crohn's disease because a drug used to treat many Crohn's patients, infliximab (Remicade®), also blocks TNF-α activity.

A major advance in unraveling the genetics of Crohn's disease occurred in 1996, when researchers identified a region on human chromosome 16 believed to include Crohn's disease genes. Other scientists, using cutting-edge genetic technology called DNA microarrays, also identified chromosome areas linked to Crohn's disease.

Research took a giant leap forward this past year with the discovery of the first susceptibility gene for Crohn's disease on chromosome 16. The impetus for this discovery was research in another field on an immune gene called *NOD1*. When a draft sequence of the

STORY OF DISCOVERY

human genome was released last year, the scientist who led the team that discovered *NOD1* noticed a very similar gene—*NOD2*—in a region of chromosome 16 previously linked to Crohn's disease. He pointed this out to a colleague who was studying Crohn's disease, and together they used her repository of DNA from 416 families with a history of Crohn's disease to identify a defective form of *NOD2* in about 15 percent of Crohn's patients. The mutated gene also is present in about eight percent of healthy people, indicating that other factors must also interact for the disease to occur. The discovery of *NOD2* mutations in Crohn's disease was validated by a second independent study using a completely different approach, known as positional cloning, to hunt for Crohn's disease genes on chromosome 16. In this second study, additional mutations in *NOD2* were found in Crohn's patients. Having one flawed copy of the gene doubles a person's chances of developing Crohn's; having two copies can increase the risk from 15 to 40 fold. Scientists are now investigating the function of the protein encoded by the *NOD2* gene, and have learned that it activates a molecular factor involved in the response to bacteria. Future studies will attempt to define how mutations in *NOD2* contribute to Crohn's disease.

Extensive research by dedicated scientists and clinicians, coupled with critical advances in technology, have provided the groundwork for extraordinary achievements in genetic research. Scientists studying animal models of Crohn's disease gained insights into the intertwined roles of the immune system of genetically susceptible individuals and naturally-occurring intestinal bacteria in promoting inflammation. The availability of the complete human genome sequence was pivotal in the identification of the first Crohn's disease gene, as was open communication between researchers working in different fields. Finding this gene is a crucial step toward conquering this disease.