Ulcerative colitis and Crohn’s disease affect as many as 1 million Americans. Unfortunately, more than 10% of these patients are very young, with an estimated 140,000 children in the United States living with inflammatory bowel disease (IBD). Not only is the overall number of patients rising, but the proportion of affected children reflects an increasingly larger share of the suffering population.

Despite a dramatic increase in knowledge over the past few decades, more detailed information about gut inflammation in the earliest stages of disease is needed. It appears that genetic predisposition and additional environmental factors (possibly bacterial factors) lead to an incorrect immune response.

Most current research has used tissue samples from adult patients or animal models to help delineate the initial inflammatory events, missing the opportunity to study the very early stages of disease development. Children are a unique study population that can provide more insight into the earliest immune response, natural history of the disease, genetic associations and environmental factors important in the development of IBD. Events directly leading to IBD, such as subclinical inflammation, environmental exposures and immunosuppressive therapy, usually have only been present for a short time in children prior to diagnosis.

Multiple studies have identified specific lymphocytes (white blood cells) that play a key role in mucosal inflammation. Different molecules, chemicals that aid in the communication between cells, have been shown to initiate and sustain mucosal injury. Recent animal studies identified a new inflammatory pathway that plays a pivotal role in early inflammation, the so called “IL-23/IL-17 axis.” In animal models, administration of IL-23 accelerates the onset of colitis, whereas neutralization will decrease inflammation, suggesting this pathway is critical for the development of autoimmune disease.

The lab of Claudio Fiocchi, M.D., in conjunction with the Department of Pediatric Gastroenterology at Cleveland Clinic, is studying this pathway in children with IBD, with the hypothesis that these molecules play a bigger role in the early stages of inflammation than in the chronic disease process.

If early immune response in IBD is proven to differ from that in longstanding inflammation, new targets for very specific disease-altering therapy will become available. These highly selective and very early therapies could alter natural progression and prevent children and adults from developing chronic disease in the future.

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Although some gene abnormalities have been identified in patients with inflammatory bowel disease (IBD), scientists believe there are more genes yet to be discovered. As these genes are identified, one very important goal will be to understand the relationship between the specific gene variations and the widely varying clinical characteristics of the disease.

Cleveland Clinic’s Digestive Disease Center is conducting an IBD Genetic Study led by Principal Investigator Jean-Paul Achkar, M.D. This study is open to Cleveland Clinic patients with the diagnosis of either Crohn’s disease or ulcerative colitis who are at least 18 years of age. A healthy person (control) not related to the patient is also asked to participate; this person should not have been diagnosed with IBD or have a family history of IBD. A spouse is often a good control person. However, the absence of an available control does not exclude patients from participating.

The goal of this study is to identify the underlying genetic factors of IBD to help find better treatments and potentially allow doctors to predict which patients are at high risk for developing IBD. Currently, nearly 1,000 people have enrolled; about 60% have IBD and the rest are unaffected controls.

Blood samples are collected from each participant in a de-identified fashion (a study number will be assigned so that only the principal investigator and research assistant can determine the person’s identity). After the DNA is extracted at the lab, the genetic makeup of the affected group will be compared to that of the unaffected group.

The goal of this study is to identify the underlying genetic factors to allow better treatments for IBD and help doctors predict who is at high risk for developing it.

If you are interested in participating or would like more information, please call 800.223.2273, ext. 55174.

Xhileta Xhaja is a clinical research assistant in Cleveland Clinic’s Department of Gastroenterology and Hepatology.
Ripka Family Database for Crohn’s Disease Research: An Update

Our team is continually striving to improve how we capture and disseminate information collected from our patients related to Crohn’s disease. Recently, our Institutional Review Board, which oversees all Cleveland Clinic studies, approved the addition of data collection for patients under the age of 18 who are seen in Cleveland Clinic’s Pediatric Gastroenterology Department. Keeping in line with the Crohn’s and Colitis Foundation of America’s Pediatric Challenges Initiative, the addition of a pediatric population to an already established and functional database may provide a resource specific to outcomes research, quality improvement and improvements in clinical care.

Outcomes research for the adult population of 1,500 database patients is commonly reported by Department research and clinical fellows, doctors who are furthering their interest in a specific field such as colorectal surgery. One such current study is investigating whether smoking increases severity of postoperative complications within 30 days of surgery; another is studying whether there is a direct association of postoperative complications in Crohn’s patients who took Remicade before surgery. Prior studies of smaller samples showed no direct association with postoperative complications. Some of these studies were presented in December at the Department’s 2nd Annual Research Day. Others will be presented at the 2008 National Digestive Disease Week in May and the June American Society of Colon and Rectal Surgeon’s Annual Scientific Symposium.

In the future, we hope to see presentations that encompass the pediatric population as well. In the meantime, we will continue to include coverage of topics as they relate to the adult and pediatric population as a way of helping our patients stay informed.

Sincerely,

The Ripka Family Database for Crohn’s Disease Research Team

For more information, please call 216.445.4148.
Complex Interactions Between the Environment, Genetics Contribute to Crohn’s Disease

By Claudio Fiocchi, M.D.

Many chronic inflammatory diseases, including Crohn's disease, are called “complex diseases” because many factors help trigger them. Crohn's disease is not due to a single culprit, but rather multiple distinct factors that must come together and interact in a certain way to trigger the disease.

Factors include a person's surrounding environment, genetic makeup (the composition of DNA), immune response (host defense mechanisms) and microbes (primarily those normally present in the intestine). This brief review will discuss current knowledge on why and how the interaction of environmental and genetic factors is believed to be critically important in causing Crohn's disease.

Studies that investigate when and where a disease occur, and who gets a disease (the so-called epidemiologic studies), have determined that Crohn's disease has not affected humanity forever, but rather has emerged in the past century. Thus, Crohn's disease can be defined as a “modern disease,” similar to other autoimmune conditions such as asthma, rheumatoid arthritis and multiple sclerosis.

Epidemiologic studies have shown that Crohn's disease was initially recognized in developed countries, e.g., Northern Europe and North America, and has only spread to the rest of the world in the past 50 years. This spread paralleled the social and economic development of populations together with

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Complex Interactions Between the Environment, Genetics Contribute to Crohn's Disease

the acquisition of a “Western” lifestyle, such as eating (more food, and more nutritious and fattening food) and behavior (smoking, stress, etc).

The same studies also showed that Crohn’s disease primarily affects educated people living in urban areas. Smoking has been associated with an increased risk of Crohn’s disease and more severe clinical manifestations, as well as the use of certain drugs. Also, an increasingly clean environment due to the routine availability of safe water, better sanitation, widespread use of vaccinations and antibiotics, and fewer infectious diseases, particularly in early life, is a factor.

In other words, as the world has become cleaner and infectious diseases have steadily declined, there has been a rise in autoimmune and chronic inflammatory diseases, including Crohn’s disease.

One possible explanation is the “hygiene hypothesis,” which says that an increasingly hygienic environment and corresponding decline in infectious diseases has lead to immune systems that are less able to cope with the challenges imposed later in life by the substances to which many people are exposed. This decreased capacity to defend ourselves causes our immune response to be less effective and, rather than mounting a strong response that eliminates an offender, keeps on fighting without ever winning, resulting in the chronic inflammation typically seen in Crohn’s disease.

Even though this theory is widely accepted, it cannot alone explain the emergence and spread of Crohn’s disease, as otherwise everyone would have some type of chronic inflammatory or autoimmune condition. Other factors must be involved.

One such factor is genetic makeup. What we are, how we behave, which diseases we get and how we respond to medications is largely determined by our genes. Genes are fragments of DNA present on the chromosomes that reside in the nucleus of all cells. Each gene is responsible for producing a specific protein, and the type and amount of this protein determines how well our body functions. A person with theoretically perfectly normal genes (no such person exists) would live a long and healthy life because all of his or her gene products would function properly. On the other hand, a person with a defective gene(s) may or may not get sick depending on whether a need arises for the protein made by his or her flawed gene.

Most autoimmune and chronic inflammatory conditions are associated with genetic defects, and this is certainly the case for Crohn’s disease. A typical example is the genetic defects (also called gene mutations or variations) of the NOD2/CARD15 gene, which is associated with Crohn’s disease of the small bowel. The protein produced by the normal gene is critical for the recognition of bacteria, and apparently patients with Crohn’s disease make proteins that recognize bacteria in a way that causes inflammation rather than protection. This is only one example of the multiple genetic defects described in Crohn’s disease patients.

Additional factors are implicated in causing Crohn’s disease, including the immune response and the gut bacteria flora, and it is now clear that this condition is not due to one cause and one mechanism, but rather multiple causes and multiple mechanisms. This explains why Crohn’s disease has been so challenging to understand and conquer.

Despite these difficulties, recent research progress has been impressive and as the different disease-associated factors become better understood, one can envision the development of custom-made therapies applicable to patients whose disease is caused by different combinations of distinct risk factors.

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Genetic factors have long been suspected of playing an important role in causing inflammatory bowel disease (IBD), ulcerative colitis and Crohn’s disease. Supporting evidence comes from population data that show differences in rates of IBD based on race and ethnic background (higher rates for Caucasians and Jewish ethnicity), the finding of familial aggregation of IBD (10% to 20% of IBD patients will have a family member with the disease) and an increased risk for IBD in identical twins compared to fraternal twins. In addition, several lines of evidence suggest a stronger genetic basis for Crohn’s disease than ulcerative colitis.

The first definite genetic defect associated with IBD, the NOD2 or CARD15 gene, was discovered in 2001. Three mutations in this gene were found to be associated with Crohn’s disease but not with ulcerative colitis. Patients carrying one of the NOD2/CARD15 mutations have a 1.5 to 3.0 fold increased risk of developing Crohn’s disease; those carrying two mutations have a 14 to 44 fold increased risk. However, NOD2/CARD15 variants only account for 20% to 30% of all Crohn’s disease cases, suggesting that other genes are involved in its development. In addition, the lack of association of this gene with ulcerative colitis indicated that separate genes cause ulcerative colitis.

The discovery of the NOD2/CARD15 gene has led to a further understanding of the alterations underlying IBD, and serves to confirm the long-suspected interplay among genes, the immune system and bacteria in the development of IBD. Studies assessing the function of mutations in the NOD2/CARD15 gene show a decreased response-ness of the immune system to bacterial products, strongly suggesting that IBD may be caused by a defective host response to intestinal bacteria.

Another advantage of genetic studies of the NOD2/CARD15 gene is that they allow researchers to determine whether IBD genes affect the clinical features of the disease. Several studies, including one in which Cleveland Clinic participated with three other U.S. centers, confirmed an association between NOD2/CARD15 mutations and Crohn’s disease localized to the bottom part of the small intestine (the ileum).

Other studies have found an association between younger age at diagnosis and complicated disease behavior in subjects with NOD2/CARD15 mutations. Together, these findings suggest that IBD susceptibility genes not only increase the risk of developing IBD but also determine the type of disease the patient will develop.

Most recently, scientific advances have allowed the performance of genome-wide association (GWA) studies, in which an analysis of genetic changes throughout the entire genetic makeup of individuals can be conducted by comparing IBD-affected subjects to people without IBD. The first gene mutation identified by this technique was in the interleukin-23 receptor (IL-23R) gene and this mutation was found to be associated with both Crohn’s disease and ulcerative colitis. These findings are of particular interest because IL-23 is regarded as a prominent mediator of inflammation. Other GWA studies have been published over the past few months identifying many other potential IBD-causing genes.

The field of IBD genetics is rapidly expanding as more genes are being identified. Further work is needed, including study of the functional consequences of mutations in these genes. Such understanding could in turn lead to new, highly targeted medical therapies. In addition, studies of how these genes affect the course of disease could help clinicians better predict disease outcome, risk of complications, need for surgery and response to therapy for individual patients.

Jean-Paul Achkar, M.D., is a member of Cleveland Clinic’s Department of Gastroenterology and Hepatology. To schedule an appointment to see him, please call 216.444.6536.
Crohn’s disease and ulcerative colitis are more common in North America and Europe than in Asia and Africa. However, in Japan, the number of patients with both Crohn’s disease and ulcerative colitis has increased remarkably (Figure, below). The incidence seems to be increased in China and Korea as well.

There are some epidemiological differences between Japanese and Caucasian Crohn’s diseases. In Western countries, Crohn’s disease is slightly more common in women than in men, but in Japan, it is more common in men, and the male-female ratio exceeds 2.

**Genetic factors**

Western studies have shown that about 20% of cases of Crohn’s disease appear to run in families. If a person has a relative with Crohn’s disease, his or her risk is approximately 10 times greater than that of the general population. Furthermore, data from the Swedish twin registry have shown that if one identical twin has Crohn’s, 58% of the other twins will also have the disease.

These results suggest a strong genetic influence on the incidence of Crohn’s disease. Studies of Western populations have shown that mutations in the NOD2 gene are associated with susceptibility to Crohn’s disease. However, NOD2 mutations are not detected in the Japanese population. A recent study found that the genetic variations in the TNFSF15 gene contribute to the susceptibility to Crohn’s disease in the Japanese and European populations.

**Environmental factors**

Many environmental factors have also been hypothesized as causes for inflammatory bowel disease. A rapid increase of inflammatory bowel disease in Japan is probably associated with Westernized lifestyle. Diets may play the most important role. In Japan, average daily fat intake was 18.3g in 1950, which was increased to 57.4g in 2000, with a significant decrease in n-3/n-6 polyunsaturated fatty acid ratio.

Furthermore, a recent Japanese study found that a higher consumption of sweets was positively associated with risk of ulcerative colitis, and a higher consumption of sweets, fats, and oils with risk of Crohn’s disease. Smoking and oral contraception have also been shown to have an association with the development of inflammatory bowel disease. The risk of a smoker developing Crohn’s disease has been about twice that of a never-smoker. In contrast, the risk of a smoker developing ulcerative colitis has been around half that of a never-smoker.

Oral contraception is associated with a small increase in risk of both Crohn’s disease and ulcerative colitis. It is unclear whether these factors are directly causal relationships or due to confounding by some factor not yet identified. Measles virus and mycobacterium paratuberculosis have been suggested as possible causes of Crohn’s disease; however, a definite relationship between these factors and Crohn’s disease remains unknown.

Both genetic and environmental factors may be invoked in the pathogenesis of inflammatory bowel disease. However, the exact cause of inflammatory bowel disease is still unknown and further research is necessary.

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