Genetics of Inflammatory Bowel Diseases (IBD): IL23R as an IBD Susceptibility Gene

Dr. Judy Cho

Dr. Judy Cho is an Associate Professor in the Department of Medicine and Genetics at the Yale School of Medicine and the Director of Yale's Inflammatory Bowel Disease Center. A leader in the field of inflammatory bowel disease (IBD) research, Dr. Cho and her colleagues are widely recognized for their 2001 discovery of the first known gene to increase susceptibility to Crohn's disease—the NOD2/CARD15 gene. Dr. Cho is the Chair of NIDDK's Inflammatory Bowel Disease Genetics Consortium Steering Committee and Principal Investigator of the Consortium's Data Coordinating Center. Recently, the NIDDK IBD Genetics Consortium identified IL-23R as another IBD susceptibility gene. Dr. Cho presented this clinical research study to the NIDDK Advisory Council at their February 2007 meeting. The following are highlights from her presentation. (Additional information on IBD-related research conducted by Dr. Cho and other NIDDK-sponsored researchers is presented in this chapter's "Story of Discovery.")

The inflammatory bowel diseases are chronic, intermittent intestinal inflammations which are thought to result from inappropriate responses by the immune system to bacteria normally found in the intestine. Symptoms include diarrhea, abdominal pain, intestinal bleeding, and, in cases of childhood onset, growth retardation. IBD occurs frequently in young people—with a peak age of onset between 15 and 30 years of age. Because IBD is largely seen in industrialized societies, some researchers have suggested that it may be associated with changes in intestinal microbial populations during the industrialization process.

The two major subtypes of IBD are ulcerative colitis (UC) and Crohn's disease (CD), which are distinguished by the area of the intestines affected. The site of inflammation with UC is restricted to the colon, or large intestine. In CD, inflammation is found in the small intestine and often affects both the small and large intestines. Ileal CD, which targets a part of the small intestine known as the ileum, is the most common form of Crohn's disease.

Although little is understood regarding its etiology, IBD is known to involve complex interactions between multiple genes, as well as the microbial environment of the intestine. Two genetic associations with IBD had been well-established, the *NOD2* gene, identified by Dr. Cho and her colleagues, and a variant in another area of the genome called *IBD5*. The discoveries of these genetic variations provided two pieces of the complex IBD puzzle, but did not fully explain the incidence of IBD. Thus, the search continued for other genes associated with this disease.

Searching for Additional IBD Genes

The prevalence of Crohn's disease is several times higher in the Ashkenazi Jewish population of European ancestry than in the non-Jewish population of European ancestry. In this genome-wide association study, over 300,000 naturally occurring genetic variations were screened in Ashkenazi Jewish and non-Jewish patients and healthy controls. These variations, known as SNPs (single nucleotide polymorphisms) are small differences in an individual's DNA sequence that can have varying disease consequences ranging from causing major genetic diseases such as cystic fibrosis or sickle cell anemia to more subtle effects that alter disease risk. SNPs are valuable disease biomarkers used in both research and clinical diagnoses.

SCIENTIFIC PRESENTATION

The study began with a genome-wide screen of non-Jewish ileal CD patient and control cohorts. Ileal CD patients were selected exclusively to minimize genetic differences within the patient cohort. The screen identified three SNPs having highly significant associations with CD. Two of the three SNPs were located in the previously identified CD susceptibility gene, *NOD2*. However, the third was located in the IL23 receptor gene (*IL23R*). Surprisingly, this uncommon gene variant was found to confer protection against CD.

Ileal CD patients of Ashkenazi Jewish ancestry and their controls were then screened for *IL23R* markers. Highly significant differences were observed in the frequency of the protective marker in the two study groups. For example, this marker was identified in only two percent of CD patients in contrast to seven percent of the controls, supporting its protective role in preventing CD.

Following the two screens, the research team conducted a study to determine the frequency of the transmission of *IL23R* markers in nuclear IBD families consisting of children who were affected by IBD (CD, UC, and indeterminate IBD) and both of their parents. The study revealed that the protective variant of *IL23R* was much less likely to be passed down from parents to their IBD-affected children. Both Jewish and non-Jewish families with this marker were protected against developing CD; however, only the non-Jewish population showed a similar protective effect against UC.

The unexpected identification of a gene variant that protects against the risk of IBD has given new insights into the molecular underpinnings of this disease. These findings substantiate a hypothesis, supported by recent immunological studies, that the *IL23R* gene is required for the manifestation of clinical IBD. Importantly, these research results also provide potential therapeutic targets for its prevention and treatment.

The Inflammatory Bowel Disease Genetics Consortium (IBDGC)

In 2002, the NIDDK established the Consortium to provide the research resources necessary to take advantage of the wealth of genetic information provided by the NIH-sponsored Human Genome Project in elucidating the disease mechanisms of IBD. The infrastructure established to accomplish the Consortium's mission includes a Data Coordinating Center, which oversees genetic analysis, database analysis, and coordination between six Genetic Research Centers. The Centers recruit patients and healthy volunteers for IBD study cohorts, submit patient blood samples and phenotype data to a repository, and conduct genetic research studies. Governance of the Consortium is provided by a Steering Committee consisting of Consortium scientists and a NIDDK health science administrator.

As Chair of the Steering Committee and head of the Data Coordinating Center and of one of the research centers, Dr. Cho has played a significant role in the development of the Consortium. In describing the Consortium's major advantages, Dr. Cho identified:

- Synergy of expertise provided by gastroenterologists who are primarily interested in IBD and geneticists whose interests include IBD and complex disorders;
- Stringent quality control attained through sample and data uniformity;
- Ability to recruit the large numbers of patients required to identify the genes responsible for IBD;
- Availability of resources necessary for high risk, high priority projects—including genetic studies of disease differences in minority populations; and
- Knowledge of priorities and opportunities provided by NIH oversight.

The Consortium has developed collaborations with outside investigators, providing valuable data, genotyping services, and research resources. For

example, immortalized cell lines are being derived from patients' blood samples. These cell lines and the DNA extracted from them will be linked to the patients' phenotypic data and stored for use in Consortium research projects. They will also be made available to the broader scientific community. Additionally, control datasets representing different populations are being analyzed and made available on the web. This approach provides major research effectiveness and cost-saving advantages for future IBD studies.

A Vision for Future IBD Research

Dr. Cho described her vision for the future of IBD research and her major priorities. These include developing models of disease risk, developing biomarkers, predicting disease course, and finding ways to prevent disease. These endeavors all have as their underpinnings the identification of the multiple genes that contribute to IBD and the elucidation of their interactions with each other and their environment. Even genes with limited direct associations with IBD may have significant biological consequences that must be considered in designing important risk models. Biomarkers that reflect genetic variation and the molecular consequences of gene expression are important research indicators of disease risk, disease prognosis, and patient response to therapies. Thus, biomarkers will serve as major drivers in the development of new approaches to the prevention and cure of IBD.

The IBD genome-wide association study presented by Dr. Cho has continued to yield important genetic discoveries. An expansion of this study identified three new IBD susceptibility genes which are described in the IBD Story of Discovery, also in this chapter.