Over 50 Genetic Factors for Ulcerative Colitis

International IBD Consortium findings are expected to increase understanding of disease pathogenesis.

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — More than 50 genetic risk factors for ulcerative colitis have now been identified by the International Inflammatory Bowel Disease Genetics Consortium, John D. Rioux, Ph.D., said at the meeting.

"The work of the International IBD Consortium has dramatically increased the number of known UC [ulcerative colitis] loci and is expected to significantly increase our understanding of disease pathogenesis that relates to both shared and UC-specific inflammatory pathways," said Dr. Rioux of the University of Montreal. The Consortium spans 15 countries and employs more than 80 clinical and basic researchers.

Genome-wide association (GWA) studies analyze "hundreds of thousands of genetic variants for thousands of patients and controls" to identify genetic risk factors, he said.

GWA studies have identified genetic risk factors for Crohn's disease. While individual studies have been successful, the statistical power for gene discovery is limited by sample size. The larger the sample size, the greater the number of genetic risk factors identified, he noted.

Previously, the Consortium performed one of the first studies to combine GWA results, and identified more than 30 risk factors for Crohn's disease.

"At that time, much less was known about the genetics of UC, with only the MHC and the IL23R gene having confirmed associations. In the last year, multiple GWAs of UC have been done and have produced 18 independent new associations. These studies provided a unique opportunity to identify a much more complete catalog of genetic risk factors," he said.

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DR. RIOUX

In the current study, results from six GWA studies of UC were combined in a meta-analysis. Data from 6,433 patients with UC and 20,999 population controls from North America and Europe were combined into a dataset.

"Out of nearly millions of polymorphisms examined," the tests ultimately revealed 75 independent genomic regions significantly associated with UC. In preliminary investigations, the meta-analysis has confirmed 18 known ulcerative colitis loci, 21 novel loci, and 4 nominally significant loci (which investigators expect to become significant upon further analyses), for a total of 43 genetic risk factors to date. Another 26 are being studied but have not yet been replicated.

"Many of the UC genetic risk factors are shared with Crohn's disease—nearly 50%—as well as other inflammatory diseases," Dr. Rioux suggested. The other inflammatory diseases include psoriasis, celiac disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and others.

"We predict there are at least 52 loci associated with UC, about 50% of which are shared with Crohn's disease and about 25% with other inflammatory diagnoses. The remainder appear to be UC-specific," he said.

"The research into the genetics of ulcerative colitis has highlighted the similarities and differences between ulcerative colitis and Crohn's disease, said Dr. María T. Abreu in an interview. "It shows us some of the explanations for why patients with ulcerative colitis who have a *J*-pouch [also called an ileal pouch–anal anastomosis] may ultimately develop Crohn's disease," said Dr. Abreu, professor of medicine and chief, division of gastroenterology, University of Miami.

The Consortium is currently testing all novel loci in an independent set of 10,000 UC patients and a similar number of population controls to confirm these findings, but even the preliminary results provide "convincing evidence," he said, of associations to genes of biological significance to disease pathogenesis: TNFRSF14, JAK2, CARD9 and others.

An analysis of the literature suggests that novel UC genes pinpoint potential molecular mechanisms. "In other words, each new UC gene contributes to the puzzle," he said.

For example, ETS1 on chromosome 11 has a profound impact on Th1 immune responses. DAP (death-associated protein) on chromosome 5 modulates mTOR (mammalian target of rapamycin) activity. WSB1 on chromosome 17 is a hedgehog-inducible ubiquitin ligase, and its loss results in spontaneous intestinal inflammation.

"We can begin to put these into biological pathways. Many genes in these pathways protect or predispose to disease, and we can identify novel targets and appropriate genetic testing within the context of clinical trials and patient selection. Our work," he added, "has just begun." ■

Irritable Bowel: 1 in 5 Patients Uses Narcotics for Bowel Pain

BY MICHELE G. SULLIVAN

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — Many patients with irritable bowel syndrome appear to be taking narcotics for bowel pain—drugs that may exacerbate their painful symptoms.

A survey of nearly 2,000 patients with irritable bowel syndrome (IBS) found that nearly 20% were currently taking a narcotic for their symptoms. "Narcotic use of that magnitude in this population has not been previously described," Dr. Spencer Dorn said at the meeting.

Patients who took narcotics were more likely to report poor health-related quality of life, to also use antidepressants and anxiolytic drugs, and to have more hospitalizations and surgeries than IBS patients who don't use narcotics.

"In the current U.S. health care system, clinicians often lack the time, infrastructure, and incentive needed to provide integrative care to patients with chronic conditions, including IBS," said Dr. Dorn. "Instead, very often physicians take the path of least resistance. Narcotic prescriptions are a quick and easy way to get patients out of the office," even though the long-term effects can be harmful.

"The broad literature suggests that narcotic use in noncancer pain syndromes may not improve functional status and help people live their lives more effectively," he said. "It is also very well known that narcotics affect bowel habits; narcotic-induced constipation is very common."

'Narcotic bowel syndrome is gaining recognition' as a consequence of long-term narcotic use.

DR. DORN

Additionally, he said, narcotics always carry a risk of drug dependence, leading to the need for increasing amounts of medication. "Narcotic bowel syndrome is gaining recognition" as a consequence of long-term narcotic use, he said. "Even though we are using narcotics to treat pain, escalating the dose may paradoxically worsen the symptoms we are trying to treat."

Dr. Dorn, of the Center for Functional GI and Motility Disorders at the University of North Carolina, Chapel Hill, and his colleagues at the International Foundation for Functional Gastrointestinal Disorders in Milwaukee, conducted an Internet survey of 1,787 adults in the United States and Canada who fit the Rome II criteria for IBS diagnosis. Results of this survey were initially published last year (J. Clin. Gastroenterol. 2009;43:541-50) and used as the basis for an informational brochure (www.aboutibs.org/pdfs/IBSpatients.pdf).

Respondents were mostly women (83%) and white (91%). IBS types were 29% diarrhea predominant, 61% mixed diarrhea/constipation/unspecified, and 10% constipation predominant. As determined by the Functional Bowel Disorder Severity Index, 31% had mild symptoms, 48% had moderate symptoms, and 21% had severe symptoms. Diagnosis of IBS was not made until a mean of almost 7 years after their symptoms began.

Most of the respondents (80%) said that pain was a major contributing factor to the severity of their IBS, with 30% saying it was the most troublesome symptom, and 78% saying their pain was continuous or frequent in the prior 6 months.

Most of the respondents were taking at least one medication, including nonnarcotic pain medications (31%), antidepressants for pain (31%), antacids (28%), antidiarrheals (24%), antispasmodics (19%), and narcotics (18%).

A regression analysis found that narcotic use was significantly associated with low health-related quality of life; rating pain as the most bothersome symptom; having a larger number of hospitalizations and surgeries; and the concurrent use of antidepressants, anxiolytics, and antacid medications.

The preferred approach to IBS treatment is a holistic one, Dr. Dorn said.

"We suggest an integrated approach in which clinicians first consider the medical and psychosocial factors that influence their patients' illness, and then address their patients' main concerns, educate them about IBS, offer strategies to enhance their self-management, and, if appropriate, address any maladaptive coping styles and the possible role of psychological stressors. This approach is often best delivered by a multidisciplinary treatment team." ■

VITALS

Major Finding: Of patients with irritable bowel syndrome, 18% were using narcotic pain medications to relieve bowel pain.

Data Source: An internet survey of 1,787 patients with irritable bowel syndrome.

Disclosures: The University of North Carolina and the International Foundation for Functional GI and Motility Disorders sponsored the study. Dr. Dorn had no relevant financial disclosures.