

Digestive Diseases

NEWS

National Digestive Diseases Information Clearinghouse

Fall 2008

Scientists Identify 21 New Genetic Loci Related to Crohn's Disease

Findings Bring Researchers Closer to Novel Treatments

A consortium of researchers from the United States, Canada, and Europe has identified 21 new genetic loci for Crohn's disease, a chronic disease of the large and small intestines. This discovery, funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health (NIH), brings the total number of known genetic loci associated with Crohn's disease to more than 30 and advances understanding of causes and potential avenues to develop new treatments.

Additional research funding was provided by British, Belgian, and French government agencies and private foundations. Results were reported in the August edition of *Nature Genetics*.

Researchers from the NIDDK Inflammatory Bowel Disease (IBD) Consortium, the Wellcome Trust Case Control Consortium, and the Belgian-French IBD Genetics Consortium combined and analyzed samples from three studies that included 3,230 people with Crohn's disease and 4,829 people without the condition. Study participants were all of European descent.

The large sample size helped researchers implicate new genetic loci in Crohn's disease whose contributions to the disease were undetectable by previous small studies. These findings enable earlier predictions of which patients are at risk for the most serious forms of the disease, thereby permitting earlier treatment to prevent complications.

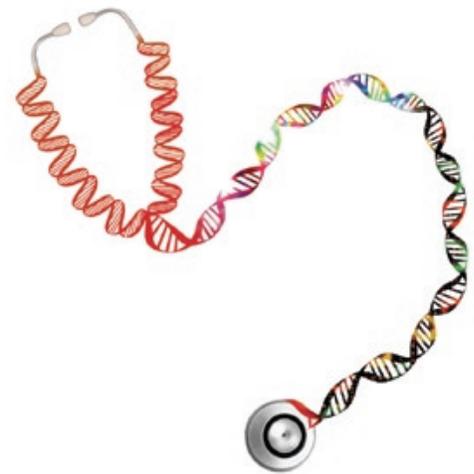


Image by Jane Ades, NHGRI

Several of the recently identified genetic loci, which were discovered through genome-wide scans, are located in genes involved in biochemical pathways promoting inflammation. Others

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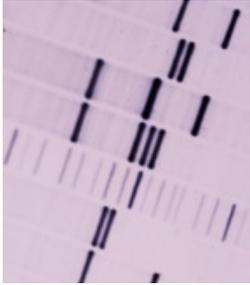


NIDDK

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“The discovery of 21 new loci for Crohn’s disease highlights the importance of large genome-wide studies in determining genes responsible for some of the most common, intractable diseases that plague millions worldwide.”

Stephen P. James, M.D.
 Division of Digestive Diseases and Nutrition
 Director, NIDDK

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are located in regions of the genome whose functions are unclear. Although the biochemical functions of these variants and how they trigger inflammation in the intestines require further study, they all represent potential targets for the development of new medications.

To confirm the findings, the researchers repeated the study in 3,664 additional people with Crohn’s disease, unaffected family members, and unaffected individuals from the general population.

“The discovery of 21 new loci for Crohn’s disease highlights the importance of large genome-wide studies in determining genes responsible for some of the most common, intractable diseases that plague millions worldwide,” said Stephen P. James, M.D., director of the Division of Digestive Diseases and Nutrition at the NIDDK.

“The NIH will continue to support this and other genetic studies, and we are excited by the prospect of what the next series of studies may uncover.”

Crohn’s disease is a chronic form of IBD that usually affects the lower part of the small intestine or the large intestine, also known as the colon. The most common symptoms of Crohn’s disease are stomach pain and diarrhea. The disease tends to run in families and is more often diagnosed in people between the ages of 20 and 30. People of Jewish heritage, particularly Ashkenazi Jews, have an increased risk of developing Crohn’s disease.

The NIDDK has a fact sheet and an easy-to-read booklet about Crohn’s disease at www.digestive.niddk.nih.gov/ddiseases/pubs/crohns and www.digestive.niddk.nih.gov/ddiseases/pubs/crohns_ez, respectively. ■



Digestive Diseases
NEWS

Digestive Diseases News, an email newsletter, is sent to subscribers by the National Digestive Diseases Information Clearinghouse (NDDIC). The newsletter features news about digestive diseases, special events, patient and professional meetings, and new publications available from the NDDIC and other organizations.

If you would like to subscribe, go to <http://catalog.niddk.nih.gov/newsletter.cfm>. You can read or download a PDF version of the newsletter at <http://digestive.niddk.nih.gov/about/newsletter.htm>.



Executive Editor: Stephen P. James, M.D.

Dr. James is the director of the Division of Digestive Diseases and Nutrition within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). As director, Dr. James oversees planning, implementation, and evaluation of a national research effort focused on gastrointestinal, pancreatic, hepatobiliary, and nutrition diseases and conditions. Before joining the NIDDK in 2001, Dr. James directed the division of gastroenterology at the University of Maryland’s School of Medicine for 10 years.



NDDIC Answers More Than 5,700 Queries in 2007

The National Digestive Diseases Information Clearinghouse (NDDIC) responded to 5,729 requests for information during calendar year 2007. The majority of these inquiries—61 percent—came from patients, their families or friends, and the general public, while 28 percent came from health care professionals, according to Kathy Kranzfelder, director of the Clearinghouse.

In 2005, only 19 percent of inquiries came from health professionals, said Kranzfelder, who presented an update on Clearinghouse activities at the NDDIC's annual Coordinating Panel Meeting in June. Last year, more than half of Clearinghouse customers—56 percent—learned about the NDDIC through the Internet. The breakdown of NDDIC customers in 2007 is depicted in the graph on the right.

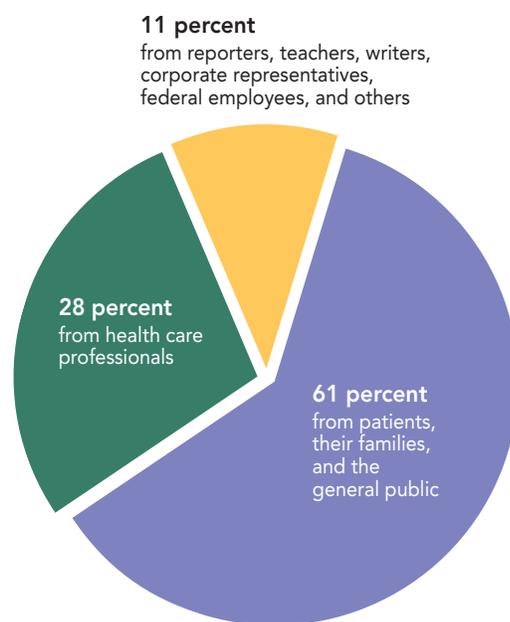
Nearly half of the Clearinghouse's requests for information still come through traditional methods—mail and telephone orders. However, online orders have increased to 47 percent last year from 29 percent in 2006. In 2007, the NDDIC website received about 365,000 visits per week.

Kranzfelder said the Clearinghouse now offers TTY telephone service, which increases accessibility to inquiry response services for people who are hearing or speech impaired.

In 2007, the most popular NDDIC publications were

- *Celiac Disease*
- *What I need to know about Irritable Bowel Syndrome*
- *What I need to know about Hepatitis C*
- *What I need to know about Celiac Disease*
- *Diverticulosis and Diverticulitis*

To visit the Clearinghouse website, go to www.digestive.niddk.nih.gov. ■



NDDIC Coordinating Panel Speaker Urges Early Detection of Colorectal Cancer

Early detection is critical for survival of colorectal cancer (CRC), the third leading cause of adult death in the United States, according to Michael B. Wallace, M.D., M.P.H., professor and vice chairman of medicine at the Mayo Clinic in Jacksonville, FL. Wallace, who spoke at the National Digestive Diseases Information Clearinghouse (NDDIC) annual Coordinating Panel meeting in June, said researchers expect that 150,000 diagnoses and 50,000 deaths will be attributed to CRC in 2008.



As with other cancers of the digestive system, the survival rate for early diagnosed CRC is stage dependent, according to Wallace. The 5-year survival rate for localized CRC is 90 percent, which is why raising awareness of early detection as an effective prevention strategy is so crucial. In most cases, CRC arises from an adenomatous polyp, a definable and detectable precancerous lesion, Wallace said. Detection and removal of a precursor lesion effectively treats the disease.

Small colon polyps and flat polyps, which may be more aggressive, present a challenge to the longstanding assumption that colonoscopy will detect all polyps and colon cancers, explained Wallace. Studies using repeat colonoscopy showed the overall “miss” rate to be 26 percent for small polyps, most of which are of unclear clinical significance.

The importance of small polyps and whether to inform patients of their presence are topics of discussion within the medical community. A study of small polyps removed during colonoscopy showed 69 percent to be adenomatous. Current standard practice with colonoscopy is to report all adenomatous polyps regardless of size and to base surveillance intervals on the number and size of adenomas.

A study at the Veterans Affairs Hospital in Palo Alto, CA, identified a new category of flat polyps previously recognized in Japan. The study found flat polyps were present in 9 percent of colonos-

copies. Flat polyps had a tenfold increase in the likelihood of being cancerous, regardless of size.

Because flat polyps often go undetected, inspection techniques using chromoendoscopy and narrow band imaging were used to find them. Flat polyps were highlighted using blue dye for easier detection. Using endoscopic resection, polyps were injected with fluid to raise them for removal. These techniques are effective and safe but require specialized training.

Joint Guidelines

Wallace said, in recent months, the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology released *Joint Guidelines for Early Detection of Colorectal Cancer and Adenomatous Polyps: 2008*. The guidelines recommended

- tests to detect cancer. These tests involve stool analysis and are minimally invasive:
 - fecal occult blood test or guaiac—recommended every year after age 50.
 - fecal immunochemical tests.
 - stool DNA, a new test recommended every 5 years after age 50. The test analyzes DNA integrity and identifies gene mutations in the progression from adenomas to cancer. Stool quantity and

EARLY DETECTION OF COLORECTAL CANCER,

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shipping requirements make the test hard to do at home. Although studies show variable test performance, the stool DNA test's sensitivity is superior to the guaiac test. More recent versions show improved accuracy, although invasive tests are better at detecting precancerous polyps. Combining both guaiac and stool DNA tests may result in improved program accuracy.

- tests to detect both cancerous and precancerous polyps. Only flexible sigmoidoscopy and colonoscopy can also treat polyps. These tests are more invasive:
 - barium enema.
 - computerized tomography (CT) colonography, also known as virtual colonoscopy. This test is a new recommendation, although this breakthrough “noninvasive” technology is not completely noninvasive. The test involves a CT scan with oral contrast, and the recommended bowel prep is similar to that of a standard colonoscopy. Patients show only minimal preference for CT

colonography over standard colonoscopy and prefer to be asleep during the test. Meta-analyses have shown that overall accuracy for detecting large polyps—greater than 10 millimeters (mm)—is reasonably good; however, for all polyps, sensitivity is variable. Accuracy is poor in small polyps—smaller than 5 mm. Overall, standard colonoscopy is more accurate in detecting both small and large polyps. If polyps are found during CT colonography, a colonoscopy is needed for polyp removal; cost implications are an issue.

With a wide range of technology available for CRC detection and colon polyp removal, there are tradeoffs between accuracy and invasiveness, Wallace noted. Research priorities include estimating progression time from small polyps to CRC, improving technologies and techniques to eliminate cases of missed polyps and adenomas, and improving the accuracy of noninvasive, low-cost, acceptable screening tests.

The NDDIC has a fact sheet in English and Spanish entitled *Colon Polyps: What You Need to Know*. To see a copy, go to www.digestive.niddk.nih.gov/diseases/pubs/colonpolyps_ES. ■

Grants Available to Research Impact of Health Communication on Dietary Behavior

The National Institutes of Health (NIH), along with the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration, has issued a funding opportunity announcement (FOA) for research projects focused on creating and executing communication strategies to change dietary behaviors to improve health.

The FOA is designed to promote interdisciplinary research at multiple levels—individual, environmental, and policy—and across diverse populations. Research targeting populations at high risk for obesity, such as children, teenagers, and minority populations, is encouraged.

The funding will be awarded as an R01 and R21 grant. The NIH R01 grant

- supports a discrete, specified, circumscribed research project
- is the NIH's most commonly used grant program
- is not limited to a specific dollar amount unless specified in the FOA
- requires advance permission for \$500,000 or more in direct costs in any year
- is generally awarded for 3 to 5 years



The NIH R21 grant

- encourages new, exploratory, and developmental research projects by supporting the early stages of project development
- is sometimes used for pilot and feasibility studies
- limits funding to 2 years
- usually limits the combined budget for direct costs for the 2-year project period to \$275,000
- generally requires no preliminary data

For complete information about applying for the R01 grant, go to www.grants.nih.gov/grants/guide/pa-files/PA-08-239.html. For more information about the R21 grant, go to www.grants.nih.gov/grants/guide/pa-files/PA-08-240.html. ■

NIH-supported Researcher Developing Celiac-safe Wheat Varieties

The National Institutes of Health (NIH) has awarded a 4-year, \$837,000 grant to Washington State University researcher Diter von Wettstein, Ph.D., D.Sc., to further his work on developing wheat varieties that people with celiac disease can safely eat.

Celiac disease is an immune reaction to gluten, a protein found in wheat, rye, and barley. An estimated 1 percent of all Americans suffer from celiac disease, though many have never been diagnosed and are not receiving treatment.

Von Wettstein and his research team have discovered a mutant form of barley that lacks gliadin-type proteins. Gliadin is the component of gluten that triggers the abnormal immune reaction of celiac disease. The discovery paves the way for development of gliadin-free wheat varieties.

In support of its research, the Washington State University team is partnering with the biotech company Arcadia Biosciences to identify specific gene mutations that affect gliadin-type proteins.

The NIH Celiac Disease Awareness Campaign provides current, comprehensive, science-based



information about the symptoms, diagnosis, and treatment of celiac disease, also known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy. For more information about celiac disease and related research, visit www.celiac.nih.gov. ■

CDAC Feature Article Highlights Celiac Disease and Reproductive Problems

Infertility, recurrent spontaneous abortion, and preterm delivery are among the reproductive problems that could affect women with celiac disease. Men with celiac disease could experience reduced fertility and sexual dysfunction.

The Celiac Disease Awareness Campaign (CDAC) has a new feature article about celiac disease and reproductive problems. The article is part of a series available on the Awareness Campaign website at www.celiac.nih.gov. These feature articles are copyright-free and can be reproduced in their entirety for use in other newsletters or websites. ■



MedlinePlus Health Information Now Available in Multiple Languages

MedlinePlus, a consumer health portal from the National Library of Medicine (NLM), part of the National Institutes of Health, now features reliable health information in many languages. The collection of health resources contains more than 2,500 links to information in 44 languages covering nearly 250 health topics.

To be included on the MedlinePlus website, the multiple-language information must be produced by the Federal Government or a U.S.-based organization such as a hospital or medical association.

Users can navigate the new collection of health information either by language or topic. The page listing the 44 languages covered in the collection is located at www.nlm.nih.gov/medlineplus/languages/languages.html. The most commonly spoken languages included on the site are Chinese, Korean, Russian, Spanish, and Vietnamese.

Links to foreign-language information can also be found on individual topic pages, such as the “Digestive Diseases” topic page at www.nlm.nih.gov/medlineplus/digestivediseases.html. MedlinePlus has information about “Digestive Diseases” in all of the languages listed in the right-hand column on that page.

Limited English Proficiency

According to a 2006 survey by the Health Research and Educational Trust of more than 850 hospitals, 80 percent of them treat patients with limited English proficiency. But despite nationwide demand, free, online consumer health information in multiple languages has not been readily available.

To be included on the MedlinePlus website, the multiple-language information must be produced by the Federal Government or a U.S.-based organization such as a hospital or medical

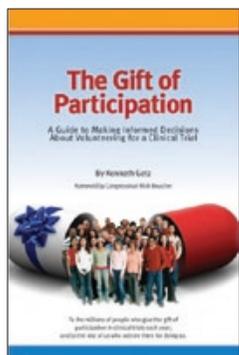


association. The information also must be current, authoritative, and appropriate for a U.S. consumer audience.

“As the population of patients and consumers with limited English proficiency increases, more health care providers, patients, and family members will need information in languages from Hindi to Tagalog,” said Paula Kitendaugh, head of the health information products unit in the NLM’s public services division. “By creating a repository of authoritative, free, online information, we hope MedlinePlus will help meet that need.” ■

Featured in the NIDDK Reference Collection

Clinical Trials



The Gift of Participation: A Guide to Making Informed Decisions About Volunteering for a Clinical Trial describes why clinical trials are conducted, why people choose to participate in them, the importance of becoming educated about clinical trials, how to locate an appropriate clinical trial, the concept of informed consent, clinical trial care and compensation, the role of institutional review boards, historical events that have shaped human subject protection, considerations for special populations, and what to do when things go wrong. The book also has nine appendices that include a glossary and a history of key regulations and guidelines affecting patient protection in clinical research.

The book's author, Ken Getz, is the founder of the Center for Information and Study on

Clinical Research Participation, which provides outreach and education to people who are considering joining a clinical trial. The 360-page book is available for \$19 at the center's website, www.ciscrp.org/e-store/books.asp.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Reference Collection is a free, online database that helps health care professionals, health educators, patients, and the general public find educational materials not typically referenced in most databases. The NIDDK does not control or endorse the information contained in this collection; the information is provided as a convenience to our visitors. To find more resources about digestive diseases, visit www.catalog.niddk.nih.gov/resources. ■

Additional Resources

Liver Disease Research

Three years after the National Institutes of Health (NIH) adopted the *Action Plan for Liver Disease Research*, the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee that developed it reported that important advances have been made toward achieving the 214 research goals outlined in the document.

Since the plan was published in December 2004, the subcommittee has followed up with yearly progress reviews. The most recent, *Progress Review for 2007 (Year Three Analysis): Action Plan for Liver Disease Research*, reported that several exciting research advances toward the Action Plan's research goals were achieved last year, including

- development of a transgenic mouse with a "humanized" liver, which has major implications for studying many liver diseases

- further work on the human liver proteome project, which is providing a complete picture of liver proteins and their structures, forms, modifications, and interactions
- a better understanding of interferon induction pathways and antiviral drug resistance associated with hepatitis C virus infection
- development of animal models and elucidation of molecular pathways that are disturbed in fatty liver disease
- development of molecular assays for diagnosis of neonatal cholestatic syndromes
- demonstration that the availability of living donor liver transplantation improves survival of patients with end-stage liver disease
- identification of genes associated with gallstone disease—genes that are linked to cholesterol metabolism and open up new therapeutic possibilities

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The 2007 Progress Review is being used by NIH Institutes and Centers and other Federal agencies and nonfederal organizations to plan liver disease research initiatives for 2008 and beyond. Researchers applying for NIH grants related to liver diseases are encouraged to reference the Action Plan and highlight how their proposed studies would address its research goals.

The Action Plan, including the process that resulted in its publication, was used as a model by the National Commission on Digestive Diseases, which is finalizing a 10-year research plan for the wider range of digestive diseases, including a chapter devoted to liver disease research opportunities that was informed by the Action Plan.

For a copy of the progress review for 2007 and the original report, go to www2.niddk.nih.gov/AboutNIDDK/ResearchAndPlanning/Liver_Disease/Action_Plan_For_Liver_Disease_Intro.htm. ■

Updated Publications

The National Digestive Diseases Information Clearinghouse has updated the following publications:

- *Barrett's Esophagus*
- *Constipation in Children*
- *Diverticulosis and Diverticulitis*
- *Pancreatitis*
- *Porphyria*
- *Primary Sclerosing Cholangitis*

These publications are available at www.digestive.niddk.nih.gov/ddiseases/a-z.asp. ■

