In 2004, the NIDDK developed an Action Plan for Liver Disease Research outlined at:


The goal of the Action Plan for Liver Disease Research is to advance research on liver and biliary diseases with the aim of decreasing the burden of liver and biliary diseases in the United States.

On 5/2/06 the NIDDK published its Year 1 Progress Review:

http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/progress_reviews.htm

The objective of the Annual Progress Review is to aid in the implementation of the Action Plan for Liver Disease Research through an ongoing assessment of progress and the need for further efforts to promote liver and biliary disease research.

The section most relevant to PSC is Chapter 9 - Autoimmune Liver Disease (PDF: 92kb, pp. 35-36)


The text of this progress review is shown below. It is broken down into short- (A), medium- (B) and long-term (C) goals. The numbers in parentheses at the end of each goal represent the estimated percent completion of each goal as of 05/02/06:

A. Short-Term Goals (1-3 years)

A1. Organize and convene an international, interdisciplinary workshop on development of animal models of autoimmune liver diseases. The NIH Workshop on Primary Sclerosing Cholangitis (PSC) in September 2005 included a comprehensive presentation on animal models in this disease. (30%)

A2. Develop multicenter networks of investigators to study natural history, pathogenesis, etiology, and therapy of autoimmune liver disease. Discussion among investigators is ongoing about the organizational and operational structure of such multicenter networks. (0%) *

A3. Define the roles of CD4+ and CD8+ T cells, other effector immunocytes, dendritic cells, and the innate immune system in liver injury in humans (and animal models) with autoimmune liver disease. Discussion among investigators is ongoing about the organizational and operational structure of such multicenter networks. (0%) *

B. Medium-Term Goals (4-6 years)

B1. Demonstrate whether high-dose urosdiol therapy is effective in retarding the progression of PSC and identify risk factors for progression and for response to treatment. The NIH sponsors a
multicenter controlled trial of high-dose ursodiol in PSC, which completed enrollment in 2005.


A similar study in Europe has demonstrated the lack of effect of high-dose ursodiol on survival and outcome (Olsson R. Gastroenterology 2005; 129:1464). (30%)

B2a. Develop sensitive and specific biomarkers for disease activity and stage in PBC and PSC. The NIH has encouraged research in this area through its initiative on "Development of Disease Biomarkers" (PA-05-098). (0%)  


B2b. Develop diagnostic criteria and standard definitions for endpoints of therapy. Discussions on developing standardized terminology and diagnostic criteria for liver and biliary diseases were started at an NIH/AASLD workshop on "Nomenclature, Diagnostic, and Outcome Criteria in Liver and Biliary Diseases" in November 2005 and at the September 2005 NIH Workshop on PSC (http://www.niddk.nih.gov/fund/other/primer-sclerosing/). (10%)


* Goal A2, probably the most important one for completing several of the medium- and long-range goals, is about to be completed for PSC, thanks to the funds and efforts of the Morgan Foundation and development of the STOPSC registry (see page 3). Goal A1 was also accomplished for PSC thanks to sponsorship by the Morgan Foundation.

References Cited


The Morgan Foundation

As described by Dr. Dennis Black at our 2006 Conference in Pittsburgh, the mission of the Morgan Foundation (The Musette and Allen Morgan, Jr. Foundation for the Study of Primary Sclerosing Cholangitis) (http://www.pscfoundation.org/) is to sponsor and facilitate both basic and clinical research to discover new treatments and ultimately a cure for primary sclerosing cholangitis. This foundation sponsored an NIH PSC Conference held in Bethesda, MD in September 2005; the summary of the conference has recently been published in Hepatology. The Morgan Foundation has a competitive grants program and has funded several PSC research projects in the last 2 years, as described at: http://www.pscfoundation.org/research.html

The Morgan Foundation has also established a PSC registry (STOPSC) [Studies of Primary Sclerosing Cholangitis] (https://web.emmes.com/study/psc/index.html) which will include PSC, autoimmune hepatitis and overlap syndrome pediatric and adult patients, and will house a database of information and tissue and DNA samples, facilitating collaborative, hypothesis-driven, multicenter research on this rare disease. Its objectives are to identify risk factors, including genetic and environmental factors, for development of PSC, and to understand the mechanisms involved in the pathogenesis of the disease. It hopes to facilitate identification of genetic factors in the predilection of the disease, disease severity, and response to treatment. Candidate genes include HLA haplotypes, CFTR, MDR3, and NOD2, as well as inflammatory mediator gene polymorphisms, and liver disease modifier genes. The STOPSC registry will also help develop diagnostic tests/approaches that can diagnose the disease at an early stage, as well as surrogate markers for severity, progression and response to treatment. The registry will assist in clarifying the relationship between pediatric and adult PSC, the natural history of the disease, the relationship to allied diseases such as inflammatory bowel disease and autoimmune hepatitis, and risk factors and markers for the development of cholangiocarcinoma. It will further facilitate the evaluation and comparison of different therapies in multicenter controlled trials. The STOPSC registry will become the major focus of the Morgan Foundation. The registry is due to open in August/September 2006, and will initially include 12 centers, all within North America (https://web.emmes.com/study/psc/about/about.html).

STOPSC Organizational Chart
The Division of Digestive Diseases and Nutrition (DDN) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invites Cooperative Agreement Applications for a single Genetic Analysis, DNA and cell line repository and Data Coordinating Center (DCC) and for multiple inflammatory bowel disease (IBD) Genetic Research Centers (GRC) to participate in the development and implementation of studies to identify genes which are associated with Crohn’s disease and ulcerative colitis. The DCC and GRCs will work together cooperatively as a Consortium. The primary objective(s) of this investigation will be identification of genes or genomic regions that are associated with increased risk of IBD and with specific phenotypic manifestations, such as early age of onset, location, complications, rate of progression, response to therapy or susceptibility to environmental risk factors. To achieve this objective, two different types of centers will form a consortium consisting of centers which will work together with staff from NIDDK to achieve the study objectives. There will be a single Genetic Analysis, DNA and cell line repository and Data Coordinating Center (DCC). This center will be responsible for the collection, management and support of analysis of both the genetic and clinical data. The DCC will coordinate communication and research with the GRCs. The DCC may apply both existing and novel methods for data collection and genetic analysis. The DCC will play a key role in the logistics of the planning and development stage. In addition to assisting the GRCs in finalizing the study protocols, the DCC will establish the data acquisition, transfer, and management system; develop procedures for ensuring subject and control confidentiality and safety; develop procedures for quality control, training, and certification; develop and produce a manual of operations; and supervise the orderly collection and transmission of data. To achieve the aims of the study, the DCC will also be responsible for the creation and maintenance of a DNA and cell line repository containing appropriate patient and control samples that are required to achieve aims of specific research studies. It is anticipated that the repository may be maintained through a contract mechanism from the DCC. In addition, the DCC may propose cost-efficient methods to provide services, such as genotyping, to GRCs. Although a DCC and GRC may exist at the same institution, the two types of centers will require separate applications and these will be evaluated independently, by criteria outlined below. The GRCs will be composed of one or more sites having investigators with expertise in genetics and inflammatory bowel disease which will participate in the collection of data and genetic materials from appropriate groups of patients and propose and execute individual research projects. It is envisioned that the GRC will need to concentrate on details of study design, including the development of phenotypic criteria and realistic estimates of the appropriate number of well-characterized selected patient, family and control subjects to achieve the goals of the study. The GRCs will have full responsibility for identifying, recruiting and enrolling the necessary number of study participants to meet the study goals and bring the study to completion. The GRCs will collect and transmit genetic, familial and clinical data as delineated in the Manual of Operation. As a part of this solicitation, each GRC will propose one or more genetic studies which are aimed at the overall objective, stated above, and which will effectively use the resources of the consortium.

An example of a recent publication from the NIDDK IBD Genetics Consortium:


Phenotype-stratified genetic linkage study demonstrates that IBD2 is an extensive ulcerative colitis locus.


OBJECTIVES: The complete elucidation of genetic variants that contribute to inflammatory bowel disease (IBD) will likely include variants that increase risk to both Crohn's disease and ulcerative colitis as well as variants that increase risk for particular phenotypic subsets. The purpose of this study was to assess phenotypic subsets that contribute to the major IBD susceptibility loci. METHODS: This linkage study encompassed 904 affected relative pairs, representing the largest combined phenotyped cohort to date, and allowing for meaningful subset analyses. Genetic linkage data were stratified by disease location and age at diagnosis. RESULTS: We establish that some loci, notably the IBD3 and chromosome 3q linkage regions demonstrate contributions from both small intestine and colon cohorts, whereas others, notably the IBD1 (NOD2/CARD15) and IBD2 regions increase risk for small intestine or colon inflammation, respectively. The strongest linkage evidence in this study was for the subset of extensive ulcerative colitis in the region of IBD2 (lod 3.27; p < 0.001). Evidence for linkage in the region of NOD2/CARD15 (IBD1) was stronger for the subset of Crohn's patients with ileal disease (lod 2.56; p = 0.035) compared to the overall Crohn's group, consistent with previous findings that NOD2/CARD15 variants are associated with ileal disease. CONCLUSIONS: Analyses incorporating disease location in IBD increase the power and enhance the accuracy of genomic localization. Our data provide strong evidence that extensive ulcerative colitis represents a pathophysiologic subset of IBD. PMID: 16542294.
**Crohn’s and Colitis Foundation of America (CCFA) Research Awards**

The Crohn’s and Colitis Foundation of America (CCFA) offers a number of research awards:

- [http://www.ccfa.org/](http://www.ccfa.org/) [then follow these links]
  - Science and Professionals
  - Research Grant Opportunities
  - Research Awards

**Senior Research Awards.** Support for established researchers who hold an MD, PhD or equivalent and are employed by a public non-profit, private non-profit, or government institution engaged in health care and/or health related research. Eligibility is not restricted by citizenship or geographically. All proposed research projects must be relevant to the inflammatory bowel diseases (Crohn’s Disease and ulcerative colitis).

**Research Training Awards.** The Foundation makes two types of research awards to candidates, including foreign scientists who are employed by a public nonprofit institution or a government institution engaged in health-related research within the U.S. and its possessions. These are our Career Development Awards and our Research Training Awards.

**Career Development Awards: Basic and Clinical Tracks.** At the time of submission, MD candidates must have at least five years postdoctoral experience (with two years of research relevant to IBD) and generally not in excess of ten years beyond the attainment of the doctoral degree, and PhD candidates must have two years of postdoctoral research relevant to inflammatory bowel disease. Awardees must devote a minimum of 80% of his/her time directly to the project.

**Research Fellowship Awards.** At the time of submission, applicants must hold an MD, PhD or equivalent with at least two years of postdoctoral experience. MDs must have two years of research experience, one year of which must be documented research experience relevant to IBD. PhDs must have one year of research experience at the time of submission. Awardee must devote a minimum of 90% of his/her time directly to the project.

**Student Research Fellowship Awards.** Up to 16 Student Research Fellowship Awards per year are available for undergraduate, medical or graduate students (not yet engaged in thesis research) in accredited North American institutions to conduct full-time research with a mentor investigating a subject relevant to IBD. The mentor may not be a relative of the applicant: applicant may not work in relative's lab. The duration of the project is a minimum of ten weeks.

*Please visit the CCFA website for further details!*

---

**Two NIH Initiatives Launch Intensive Efforts to Determine Genetic and Environmental Roots of Common Diseases**


The Department of Health and Human Services (HHS) has announced the creation of two new, closely related initiatives to speed up research on the causes of common diseases such as asthma, arthritis and Alzheimer’s disease.

One initiative boosts funding at the National Institutes of Health (NIH) for a multi-institute effort to identify the genetic and environmental underpinnings of common illnesses. The other initiative launches a public-private partnership between NIH, the Foundation for the National Institutes of Health (FNIH) and major pharmaceutical and biotechnology companies, to accelerate genome association studies to find the genetic roots of widespread sicknesses.

---

### Other NIH Funding Opportunities

NIH funds research on ‘Pilot And Feasibility Clinical Research Studies In Digestive Diseases And Nutrition (PA-06-301)’. The goal of this initiative is to encourage pilot and feasibility clinical and epidemiological research studies of new therapies or means of prevention of digestive and liver diseases and nutritional disorders associated with digestive and liver diseases.


NIH also funds research on ‘Diet-Induced Changes in Inflammation as Determinants of Colon Cancer’ (PA-05-125). Inflammation is a natural response of the human body to tissue injury or infection, but can, in some normal and abnormal conditions, be acute or chronic and result in serious complications, including colon cancer. The various checks and balances within the inflammatory process may be compromised by the quantity and duration of the insult, or by a host of genetic and environmental factors including diet. Several epidemiological and pre-clinical studies reveal that specific bioactive food components can suppress colonic inflammation as well as reduce colon cancer risk. Nevertheless, it remains unclear whether these diet-induced shifts in the inflammatory process account for their anti-tumorigenic properties in colon cancer. This PA is designed to foster innovative research that will identify and characterize diet-induced changes in inflammation and colon cancer risk.


To search for other funding opportunities at NIH, please visit [http://grants.nih.gov/grants/guide/](http://grants.nih.gov/grants/guide/) and enter your search criteria.
American Liver Foundation

2007 Special Research Initiative: Primary Sclerosing Cholangitis (PSC) Postdoctoral Research Fellowship
http://www.liverfoundation.org/db/grants/137

OVERVIEW
The American Liver Foundation (ALF) Special Research Initiative (SRI) Primary Sclerosing Cholangitis (PSC) Postdoctoral Research Fellowship is a one-year salary supplement to encourage the development of individuals with research potential who require additional research training and experience. The award is intended to support investigational work relating to liver physiology and disease in order to prepare the awardee for a career of independent research.

The Postdoctoral Research Fellowship Award is designed as a supplement to augment NIH or non-federal fellowship stipends and will not be awarded to an applicant who has no other source of research salary support.

ELIGIBILITY
In order to be eligible for this award, the applicant must conform to the following guidelines:

The applicant must be sponsored by a public or private non-profit institution accredited in the United States, Canada or Mexico engaged in health care and health-related research.

The applicant must be in his/her first or second year of a Postdoctoral Research Fellowship at the time of application. Individuals with more than two years of postdoctoral research training are ineligible.

The applicant must be sponsored by a research mentor.

SALARY/FUNDING
Payment is made directly to the applicant and not the institution.

Funding will be in the amount of $12,500 for one year.

IMPORTANT DATES
Deadline for Submission: 5:00PM EST October 2, 2006
Notification Date: March 2007
Grant Start Date: July 1, 2007

Original and 24 copies of the completed application should be sent to:

American Liver Foundation
Research Department / PSC Special Research Initiative
1425 Pompton Avenue, Suite 3
Cedar Grove, NJ 07009

For additional information, contact Joan Gallagher:
jgallagher@liverfoundation.org

Additional research grants offered by the American Liver Foundation can be found at:

http://www.liverfoundation.org/db-list/grants/0/descend/ID/Validated
PSC Partners Seeking a Cure Foundation Funding Proposals

The PSC Partners Seeking a Cure Medical/Scientific Advisory Committee has been asked to make recommendations to the PSC Partners Seeking a Cure Board concerning how best to utilize our funds to support PSC research. It is the responsibility of this committee to come up with a plan for how to use our dollars wisely, and meet our stated goal of raising funds "with which to research the causes and cures of PSC".

The Medical/Scientific Advisory Committee is currently considering three proposals as to how we might begin to distribute our funds and impact PSC research:

**Proposal 1. Support the STOPSC registry.**
**Proposal 2. Give an annual prize for best PSC research at a national liver meeting.**
**Proposal 3. Develop a competitive grants program to support PSC research fellows.**

Each of these proposals is outlined below. The Medical/Scientific Advisory Committee would like to hear YOUR opinions about these three proposals before making recommendations to the PSC Partners Seeking a Cure Board. Members of the PSC Support Group (Yahoo) can voice their opinions by voting for or against each of these proposals in a "poll" posted on the PSC Support Group (Yahoo) message board:

http://health.groups.yahoo.com/group/psc-support/surveys?id=2299168

Alternatively, please send your comments and suggestions by e-mail to David Rhodes: rhodesdavid@insightbb.com

---

**Proposal 1. Support the STOPSC registry.**

As background to this proposal, it is noteworthy that the 2004 NIH/NIDDK Action Plan for Liver Disease Research recognized that a critically important goal is to develop multicenter networks of investigators to study natural history, pathogenesis, etiology, and therapy of autoimmune liver disease. This goal is about to be met for PSC, thanks to the funds and efforts of the Morgan Foundation and development of the STOPSC registry (described on p. 3). This registry is due to launch in August/September 2006.

The STOPSC registry will serve as a repository for patient data, blood samples, liver tissue and DNA, and will allow approved investigators to answer questions related to the epidemiology, patient characteristics and genetics of PSC. Patients from the database will be available for entry into multicenter therapeutic trials to treat PSC. PSC experts from all over the world agree that the registry is the single most important endeavor to really make progress with ultimately finding a cure for this disease. STOPSC has become the major focus of the Morgan Foundation.

The registry is run under contract with the EMMES corporation in Rockville, MD. The costs of the registry is expected to be $800,000 - $1,000,000 per year. There are 12 centers currently involved, all in North America:

1. Children's Hospital Boston - Boston, MA
2. Children's Memorial Hospital - Chicago, IL
3. Harvard Medical School - Boston, MA
4. Hospital for Sick Children, Toronto - Toronto, Ontario, Canada
5. LeBonheur Children's Medical Center - Memphis, TN
6. Mayo Clinic - Rochester, MN
7. Mount Sinai School of Medicine - New York, NY
8. Tufts University School of Medicine - Boston, MA
9. University of California, San Francisco - San Francisco, CA
10. University of Cincinnati - Cincinnati, OH
11. University of Colorado - Denver, CO
12. Virginia Commonwealth University - Richmond, VA

Each center will have a principal investigator (P.I.), and each P.I. will receive $20,000 per year compensation [larger centers may require larger compensation]. In addition, each center will be paid $200 per patient entered into the registry, with $100 per year follow-up. This includes costs of entering all of the data for each patient and completing all of the necessary forms. The Morgan Foundation would like to see the number of participating centers grow over time.

The Morgan family has committed $2 million to fund this registry for the first 2 years, but has made further funding contingent upon the registry finding additional support.

PSC Partners Seeking a Cure might consider contributing funds directly to support this STOPSC registry. This would make an important statement to our donors and to the liver disease research community (including NIH/NIDDK) that our foundation supports the goals and objectives of STOPSC, and sees STOPSC as a key to advancing our understanding of factors contributing to this disease.
Proposal 2. Give an annual prize for best PSC research at a national liver meeting.

This would increase awareness of our organization in the liver research community. Dr. Nick LaRusso presented the idea of a named annual prize. As he is the next AASLD president, he would be willing to help implement this proposal. A possible name for the prize would be "Partners Seeking a Cure Prize for Scholarly Contributions to the field of Primary Sclerosing Cholangitis", or "P$C" for short.

Proposal 3. Develop a competitive grants program to support PSC research fellows.

Draft of a possible grant program:

The PSC Partners Seeking a Cure foundation is a non-profit 501(c)3 foundation whose mission is to provide research, education, and support for people affected by Primary Sclerosing Cholangitis (PSC). The PSC Partners Seeking a Cure foundation offers grants to support PSC research fellows (an M.D. and/or Ph.D. research fellow) to conduct research that addresses an important and novel, basic or clinical research question related to PSC and closely allied diseases, such as inflammatory bowel diseases (IBD) (ulcerative colitis (UC) or Crohn's disease). The applicant must be a research fellow in an academic institution, working under the guidance of a mentor with research experience in PSC or allied diseases. The goal of funding is to help encourage young investigators to conduct research in a promising new area. Funding is limited to $20,000 per year for 1 year.

The PSC Partners Seeking a Cure foundation is particularly interested in funding research projects that have the potential to discover a cure for this disease, and/or identify novel therapies that may significantly delay time to liver transplantation, and/or prevent disease recurrence following liver transplantation. The foundation recognizes that much fundamental research is necessary to discover the environmental factors which may trigger this disease in genetically susceptible individuals, and thus the foundation would like to encourage research proposals aimed at identifying the gene-environment interactions contributing to disease initiation and progression. The foundation recognizes that studies with animal models may be appropriate to address these fundamental questions. The foundation is interested in funding research that explores PSC-related diseases (such as inflammatory bowel disease (IBD) (ulcerative colitis (UC) or Crohn's disease)) in ways that they impact, enable, or perhaps cause PSC. The foundation encourages research that will be complementary to the goals and objectives of the North American Adult and Pediatric PSC Registry (STOPSC) registry:

https://web.emmes.com/study/psc/about/about.html

Application Procedure

The application forms and instructions can be obtained from the PSC Partners Seeking a Cure Foundation web site (http://www.pscpartners.org) There are no specific deadlines for application submission. One copy of each full application must be submitted electronically in the English language, and in portable document format (.pdf) to: pscpartners@yahoo.com. Any revised application must include a point-by-point response to the comments of the reviewers of the original proposal.

Application Instructions

The PSC Partners Seeking a Cure foundation application form must be used. This form is available as a Microsoft Word document for download from the PSC Partners Seeking a Cure foundation web site. The application should be typed in the English language, and the pages must be numbered. The instructions below should be followed:

1. Face Sheet (self-explanatory).
2. Budget.
   The Scientific Advisory Committee may exercise discretion in the approval of the expenditure of funds, but since these are small research grants, they are primarily intended only to support the purchase of consumable research supplies (e.g. glassware, chemicals, enzymes, etc.) to conduct PSC research. Indirect costs (overhead), and salaries are not allowed.
   Items to be purchased should be briefly explained and justified.
4. Letter of Recommendation from the Fellow's Mentor.
5. Project Description.
   This segment of the proposal should be no longer than 5 pages. Type may not be smaller that 10 point. There may be no more than 15 characters per inch. No more than 6 lines of type may be within a vertical inch. Use the following format:
   5A. Project Summary - Approximately 250 words.
   5B. Specific Aims.
   5C. Background and Significance.
   5D. Preliminary Data.
   5E. Research Plan (include materials and methods, interpretation of data, anticipated results, potential problems, and alternative approaches).
   5F. Any revised application must include a point-by-point response to the comments of the reviewers of the original proposal.
7. Facilities and Equipment.
8. If the study includes human subjects, proof of
One of our foundation goals is to increase organ donor awareness. We encourage U.S.A. readers to visit www.donatelife.net and click on their state. This site gives a state by state guide to the organ donation process. This would be a good place for our members to start thinking about how to help locally, if they are interested. “While donated organs and tissue are shared at the national level, the laws that govern donation vary from state to state. Therefore, it is important for you to know what you can do to ensure your decision to be a donor is carried out.”

The following article was published in Time Magazine (mid-Atlantic edition) earlier this year:

http://www.pscpartners.org/Time-Shepherd.pdf

This article is reprinted with permission from Ken Shepherd and Time Magazine. Congratulations Ken and Patty!

Because the original article is a very large file (2.5 MB) it will have a long download time if you are using a dial-up modem.
I am pleased to announce that planning for next year’s conference is progressing well. Our third annual conference for PSCers and caregivers will take place in Denver the weekend of April 13-15, 2007. The conference will be held at the Hyatt Regency Tech Center in southeast Denver. It’s a beautiful hotel with a lap pool and fitness center for our energetic attendees. Check out the facility at www.hyattregencytechcenter.com. There is easy access from Denver International Airport via shuttle. We were able to secure a wonderful group rate of $79 per room per night for our block of rooms. You may start reserving your rooms now by calling the reservation department at 800 233-1234 or locally at 303 779-1234. In order to receive the $79 rate, be sure to tell them that:

1. You are part of the PSC Partners Seeking a Cure conference  
2. It is the Hyatt Regency Tech Center (NOT the two Hyatt hotels downtown.)

If you prefer, you can book your room online by going to www.techcenter.hyatt.com. Select your check-in and check-out dates. Under Group/Corporation #, type “G-4LIV”. Then click “Check Availability” and the $79 group rate should come up and be ready to book. If you have any problems reserving your hotel room, feel free to contact me at pscpartners@yahoo.com.

Don and I are still meeting with Dr. Greg Everson at the University of Colorado Health Sciences Center to put together a fantastic slate of speakers, who will cover a wide variety of PSC topics. As always, after each group of speakers, we will have a question and answer session for the attendees’ participation. In addition to our speakers from the University of Colorado Health Sciences Center, we have confirmed three out of state speakers: Dr. John Vierling, Director of Liver Health and Chief of Hepatology at the Baylor College of Medicine and Current President of AASLD (American Association for the Study of Liver Diseases, Dr. Douglas Labrecque, Director of Hepatology at the University of Iowa, and Dr. Gregory Fitz, Chairman of Department of Internal Medicine at UT Southwestern.

I think that you will especially enjoy several interactive sessions:

a) Question and answer panel on Social and Financial Issues Related to PSC. The panelists will include a social worker, hepatologist, transplant co-ordinator, pharmacist, and a financial advisor for transplant patients.

b) Question and answer panel on all aspects of liver transplantation (living donor liver transplant versus cadaveric, transplant costs, UNOS allocation system, etc.)

c) Breakout sessions at the end of the day Saturday with a choice of:
   1. Pediatric PSC session with pediatric hepatologists from Children’s Hospital in Denver
   OR
   2. Session on Complementary Alternative Therapies for PSC with an acupuncturist, naturopath, yoga instructor, meditation instructor, etc.)

As soon as we have confirmed all our speakers and topics, we will post conference registration information.

If you want to think about making flight arrangements, we will follow the same time schedule as our past conferences. Friday night, we’ll have a welcome reception from 5:30-7:30 p.m. Saturday, we’ll have a full day of presentations followed by a banquet in the evening. As of now, Chris Klug is planning to be our keynote speaker on Saturday evening again. Sunday’s sessions will end at noon.

I hope that you will all think seriously about joining us at our 2007 conference. Start saving your money now! Those of you who have attended our first two conferences know what an uplifting weekend this is for everyone involved. In addition to the medical knowledge that we all acquire, the friendships that we make with other PSCers and caregivers carry us far. I’m already looking forward to seeing my old friends and to meeting new PSCers and caregivers.

Together in the fight, whatever it takes!

Ricky Safer
### IN HONOR OF:

<table>
<thead>
<tr>
<th>DONOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denise Boyd</td>
</tr>
<tr>
<td>Louise and Orville Robbins</td>
</tr>
<tr>
<td>Samantha Wente</td>
</tr>
<tr>
<td>Serenity Farm Landscaping</td>
</tr>
<tr>
<td>Firstgiving Inc.</td>
</tr>
<tr>
<td>Steven Rhodes</td>
</tr>
<tr>
<td>Claudia Ortiz and Andrew Hanson</td>
</tr>
<tr>
<td>Judy and Dave Rhodes</td>
</tr>
<tr>
<td>Susan Malat</td>
</tr>
<tr>
<td>Eileen and Dan Langer</td>
</tr>
<tr>
<td>Joy and Jeremy Judkowitz</td>
</tr>
<tr>
<td>Goldman Sachs Matching Gifts</td>
</tr>
<tr>
<td>William F. Bria</td>
</tr>
<tr>
<td>Darcy Ward</td>
</tr>
<tr>
<td>Lee and Bill Bria</td>
</tr>
<tr>
<td>Joe Warmbrodt</td>
</tr>
<tr>
<td>Christine and Robert Warmbrodt</td>
</tr>
<tr>
<td>Mike Zaloudek</td>
</tr>
<tr>
<td>Dr. Edward Miller</td>
</tr>
<tr>
<td>Scitor Corporation</td>
</tr>
<tr>
<td>Josh Mletic</td>
</tr>
<tr>
<td>Harriet Raboy</td>
</tr>
<tr>
<td>Joan Gross</td>
</tr>
<tr>
<td>Jesse Fraser</td>
</tr>
<tr>
<td>Deanna Webb</td>
</tr>
<tr>
<td>Joey Hatchett</td>
</tr>
<tr>
<td>Patricia Merrill</td>
</tr>
<tr>
<td>Zach Nesler</td>
</tr>
<tr>
<td>Debra Nesler</td>
</tr>
<tr>
<td>PSC Partners Seeking a Cure</td>
</tr>
<tr>
<td>Arne Myrabo</td>
</tr>
<tr>
<td>Vel Senthil</td>
</tr>
<tr>
<td>Peggy Caffrey</td>
</tr>
<tr>
<td>Umesh Agarwal</td>
</tr>
</tbody>
</table>

### IN MEMORY OF:

<table>
<thead>
<tr>
<th>DONOR:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Rogers</td>
</tr>
<tr>
<td>Laura and Edward Maloy</td>
</tr>
<tr>
<td>Norma Neway</td>
</tr>
<tr>
<td>Sima and Clifford Malat</td>
</tr>
<tr>
<td>Linda Kendrick</td>
</tr>
<tr>
<td>Ricky and Don Safer</td>
</tr>
<tr>
<td>JoAnne Litvak</td>
</tr>
<tr>
<td>Joyce and Dick Suckerman</td>
</tr>
<tr>
<td>Cindy and Mike Goldman</td>
</tr>
</tbody>
</table>

Thank you to our new bronze level sponsors:

- Dr. Edward Miller
- Goldman Sachs Matching Gifts
- Eileen and Dan Langer
- Deanna Webb

---

**Revised PSC Brochure**

We would like to express our thanks to Sue Safer for revising and redesigning our brochure: “Living with Primary Sclerosing Cholangitis (PSC)”.

To order printed copies of the brochure, please send an e-mail with your name, mailing address and desired quantity to Barb Henshaw at: pscbrochures@yahoo.com

If requesting more than 50 brochures, please let us know how you plan to distribute them. Please allow 1-2 weeks for delivery.

http://www.pscpartners.org/PSCBrochure.pdf

**Living with Primary Sclerosing Cholangitis (PSC)**

**Making Donations to PSC Partners Seeking a Cure**

Tax-deductible donations can be sent to:

**PSC Partners Seeking a Cure**

5237 So. Kenton Way
Englewood, CO 80111

with a check made out to:

**PSC Partners Seeking a Cure**

Alternatively, donations can be made on-line via PayPal ([https://www.paypal.com](https://www.paypal.com)) to pscpartners@yahoo.com. Please include a note to indicate whom the donation is in honor and/or in memory of, and your return address.
Recent Developments in Inflammatory Bowel Disease Genetics

Researchers continue to make progress in understanding the complex genetics of inflammatory bowel disease. During the last few months, many articles and reviews were published, and abstracts of these are shown on the following pages (p. 12-16). Significant new developments include:

- the identification of a chromosome 8 gene-cluster polymorphism with low beta-defensin 2 gene copy number that predisposes to Crohn’s disease (Fellermann et al., 2006).
- the identification of CARD8 (TUCAN) as a candidate gene for the IBD gene localized on chromosome 19q (McGovern et al., 2006).

While there continues to be controversy concerning the role of DLG5 in IBD (Friedrichs and Stoll, 2006) and there is debate as to whether the polymorphisms in SLC22A4 (OCTN1) and SLC22A5 (OCTN2) are solely responsible for the IBD5 gene on chromosome 5 (Silverberg, 2006), genetic studies continue to support the association of NOD2/CARD15, tumor necrosis factor-alpha (TNFa), the human leukocyte antigen (HLA) complex, and multidrug resistance 1 (MDR1) with IBD in some (but not all) populations/ethnic groups (Torkvist et al., 2006; Fidder et al., 2006; Tremelling et al., 2006; Ahmad et al., 2006; Annese et al., 2006; Yang et al., 2006; Oostenbrug et al., 2006). There is hope that these developments will soon lead to individual management of patients (Torok et al., 2006).

Defensins are endogenous antimicrobial peptides that protect the intestinal mucosa against bacterial invasion. It has been suggested that deficient defensin expression may underlie the chronic inflammation of Crohn disease (CD). The DNA copy number of the beta-defensin gene cluster on chromosome 8p23.1 is highly polymorphic within the healthy population, which suggests that the defective beta-defensin induction in colonic CD could be due to low beta-defensin-gene copy number. Here, we tested this hypothesis, using genomewide DNA copy number profiling by array-based comparative genomic hybridization and quantitative polymerase-chain-reaction analysis of the human beta-defensin 2 (HBD-2) gene. We showed that healthy individuals, as well as patients with ulcerative colitis, have a median of 4 (range 2-10) HBD-2 gene copies per genome. In a surgical cohort with ileal or colonic CD and in a second large cohort with inflammatory bowel diseases, those with ileal resections/disease exhibited a normal median HBD-2 copy number of 4, whereas those with colonic CD had a median of only 3 copies per genome (P=.008 for the surgical cohort; P=.032 for the second cohort). Overall, the copy number distribution in colonic CD was shifted to lower numbers compared with controls (P=.002 for both the surgical cohort and the cohort with inflammatory bowel diseases). Individuals with <=3 copies have a significantly higher risk of developing colonic CD than did individuals with >4 copies (odds ratio 3.06; 95% confidence interval 1.46-6.45). An HBD-2 gene copy number of <4 was associated with diminished mucosal HBD-2 mRNA expression (P=.033). In conclusion, a lower HBD-2 gene copy number in the beta-defensin locus predisposes to colonic CD, most likely through diminished beta-defensin expression. PMID: 16909382.


Background and aims: The identification of the association between Crohn’s disease (CD) and NOD 2(CARD15) confirmed both the heritability of CD and highlighted the role of the NFkB pathway in disease pathogenesis. Other susceptibility loci exist including genetic variants at the IBD5 locus, NOD1 and TNFSF15. TUCAN (CARD8) is located beneath a CD peak of linkage on chromosome 19q. TUCAN is expressed in the gut and is a negative regulator of NFkB making it an excellent candidate gene for gastrointestinal inflammation.

Methods: Ten SNPs across TUCAN were genotyped in 365 controls and 372 CD and 373 ulcerative colitis cases. A diagnostic panel for CD was constructed using smoking status and TUCAN, NOD2, IB5, NOD1 and TNFSF15 data.

Results: We demonstrate significant association between a SNP that encodes a STOP codon at codon 10 of TUCAN and CD (OR 1.35, p = 0.0083). The association was more pronounced with disease affecting sites other than the colon (OR 1.50) and NOD2 negative CD (OR 1.49). Combination of these data with smoking, NOD2, IB5, NOD1 and TNFSF15 status demonstrated very strong associations with Crohn’s disease and high sensitivities (96.3%), specificities (99.4%) and likelihood ratios (12.8) for Crohn’s disease although further work will be needed before this model can be translated into direct clinical utility.

Conclusions: We have demonstrated an association between a likely functional polymorphism in TUCAN and Crohn’s disease. The combination of this data in a genetic panel suggests that clinicians may soon be able to translate genetic advances into direct benefits for patients.

Recent Developments: Genetic variants and the risk of Crohn's disease: what does it mean for future disease management? Torok HP, Glas J, Lohse P, Folwaczny C

Genetic research in inflammatory bowel disease, especially in Crohn's disease, has made significant progress during recent years. There have been > 10 total genome scans that have been performed, and susceptibility loci on several chromosomes have been identified. Together with candidate gene studies, these scans have led to the identification of several susceptibility genes, with CARD15 being the most important. These genetic data have already provided important insights into the pathophysiology of inflammatory bowel disease and are stimulating future research. On the other hand, genotype-phenotype associations have illustrated the heterogeneous nature of the disease. Although the clinical application of this knowledge is so far limited, there is significant optimism that an individual management of patients based on genetic data will be possible in the near future. PMID: 16872262.
The human leucocyte antigen (HLA) complex on chromosome 6p21.3 is the most extensively studied genetic region in Inflammatory bowel disease (IBD). Consistent evidence of linkage to IBD3 (6p21.1-23), an area which encompasses the HLA complex, has been demonstrated for both Crohn's disease and ulcerative colitis, and a number of replicated associations with disease susceptibility and phenotype have recently emerged. However, despite these efforts the HLA susceptibility gene(s) for IBD remain elusive, a consequence of strong linkage disequilibrium, extensive polymorphism and high gene density across this region. This article reviews current knowledge of the role of HLA complex genes in IBD susceptibility and phenotype, and discusses the factors currently limiting the translation of this knowledge to clinical practice. PMID: 16773677.

In 2004, an association of genetic variation in the discs large homolog 5 (DLG5) gene with inflammatory bowel disease (IBD) was described in two large European study samples. The initial report of DLG5 as a novel IBD susceptibility gene sparked a multitude of studies investigating its effect on CD and IBD, respectively, leading to controversial findings and ongoing discussions concerning the validity of the initial association finding and its role in the aetiology of Crohn disease. This review aims to summarize the current state of knowledge and to place the reported findings in the context of current concepts of complex diseases. This includes aspects of statistical power, phenotype differences and genetic heterogeneity between different populations as well as gene-gene and gene-environment interactions. PMID: 16773680.

Crohn's disease and ulcerative colitis are inflammatory disorders of the gastrointestinal tract with a substantial heritable component. The IBD5 region on chromosome 5q31 is one of only two loci widely confirmed to be associated with Crohn's disease in multiple independent cohorts. Although many populations have demonstrated association with IBD5, there remains uncertainty as to the causal variant within the region. A recent report identified polymorphisms in SLC22A4 (OCTN1) and SLC22A5 (OCTN2) as being responsible for the IBD5 association, however, these findings have not been replicated. This review discusses the data evaluating the IBD5 locus and the OCTN genes and their relationship to inflammatory bowel disease. Several other genes, including IRF1 and P4HA2 may be equally as likely to contain the IBD5 causal variant as the OCTN genes. PMID: 16773684.

The MDR1 gene is an attractive candidate gene for the pathogenesis of inflammatory bowel disease (IBD) and perhaps response to therapy, with evidences at both functional and genetic levels. Its product, the P-glycoprotein (P-gp) functions as a transmembrane efflux pump thus influencing disposition and response of many drugs, some of whom (i.e. glucocorticoids) central to IBD therapy. In addition P-gp is highly expressed in many epithelial surfaces, including gastrointestinal tract (G-I) with a putative role in decreasing the absorption of endogenous or exogenous toxins, and perhaps host-bacteria interaction. Many genetic variations of MDR1 gene has been described and in some instances evidences for different P-gp expression as well as drugs metabolism have been provided. However data are often conflicting due to genetic heterogeneity and different methodologies employed. Perhaps the greatest piece of evidence of the physiological importance of P-gp in the G-I tract has come from the description of the mdrl knock-out mouse model, which develops a spontaneous colitis in a specific pathogen-free environment. Studies investigating MDR1 gene polymorphism and predisposition to IBD have also shown conflicting results, owing to the known difficulties in complex diseases, especially when the supposed genetic contribution is weak. In this study we have undertaken a meta-analysis of the available findings obtained with two SNPs polymorphism (C3435T and G2677T/A) in IBD; a significant association of 3435T allele and 3435TT genotype has been found with UC (OR = 1.17, P = 0.003 and OR = 1.36, P = 0.017, respectively). In contrast no association with CD and the G2677T/A polymorphism could be demonstrated. PMID: 16773678.

The chronic inflammatory bowel diseases Crohn's disease and ulcerative colitis are common causes of gastrointestinal disease in northern Europe, affecting as many as one in 250 people. Although mortality is low, morbidity associated with these diseases is substantial. We review the recent advances in the genetics of inflammatory bowel disease, with particular emphasis on the data that have been generated since the discovery of the CARD15 (NOD2) gene in 2001. PMID: 16631883.
To date, three loci have been validated to confer susceptibility to inflammatory bowel disease (IBD): the CARD15/NOD2 gene, the disc large homolog 5 gene (DLG5), and the IBD5 locus on 5q31 (IBD5). We have explored the possibility that these loci may also be associated with susceptibility to two other chronic inflammatory diseases, multiple sclerosis (MS) and systemic lupus erythematosus (SLE). As the CARD15 risk alleles had previously been assessed in our collection of 496 MS trios, we focused our efforts on the DLG5 risk allele and the IBD5 risk haplotype (IBD5) for MS. While there is no evidence of association within our MS sample with either of these polymorphisms, screening of 1027 subjects with SLE suggests that IBD5 (risk) may have a modest contribution to disease risk in the subset of SLE subjects without lupus nephritis. In addition, a pooled analysis of existing published and unpublished data in 1305 cases of SLE genotyped for the CARD15 risk alleles suggests that only the CARD15 (908R) IBD risk allele may have a strong effect on risk of SLE. Our data, therefore, suggest that both the CARD15 gene and the IBD5 locus may have a role as general susceptibility loci for certain common, genetically complex inflammatory diseases.


Objective. Crohn's disease (CD) is a chronic inflammatory bowel disorder caused by environmental and genetic factors. Mutations in the CARD15 gene have been associated with CD. No previous case-control CARD15 study has been performed in the Swedish population. Material and methods. The study comprised of 321 individuals: 178 with CD and 143 healthy controls (HCs), all from Stockholm County. All were genotyped for the three main CD-associated CARD15 variants (R702W, G908R and 1007fs) and phenotypic associations were investigated. Results. The allele frequencies of the R702W variant (4.5% CD versus 0.7% HC, p = 0.008, OR = 6.8) and the G908R variant (2.0% CD versus 0% HC, p = 0.045) were more common in CD patients than in controls. No significant difference in 1007fs variant allele frequency was found between CD patients and controls (2.0% CD versus 1.7% HC, p = 0.8, OR = 1.1). Carriage of CARD15 variants was more common in the CD patients than in controls (15.2% CD versus 4.2% HC, p = 0.001, OR = 4.1, population attributable risk (PAR) = 11.4%). Genotype-phenotype analysis demonstrated that CARD15 variants were associated with ileal disease (p = 0.0006, OR = 9.3, CI = 2.2-34) and protective for colonic CD (p = 0.01, OR = 0.18). An association between CARD15 variants and ileal CD (p = 0.004, OR = 6.6) was confirmed by multivariate analyses. Conclusions. The CARD15 variants R702W and G908R, but not 1007fs, are associated with susceptibility to CD in Stockholm County. Genotype-phenotype analysis shows an association with ileal CD. The contribution of these CARD15 mutations in Swedish CD patients overall is low in relation to studies elsewhere in Central Europe and North America, but is consistent with emerging data from elsewhere in Scandinavia and in Northern Europe. PMID: 16716969.


BACKGROUND:: Genetic variants in DLG5, which encodes a scaffold- ing protein on chromosome 10q23, and tumor necrosis factor (TNF)-alpha, encoding a proinflammatory cytokine on chromosome 6p, have recently been reported to be associated with inflammatory bowel disease (IBD). We studied these variants to seek evidence of association with IBD in a large independent dataset. METHODS:: We genotyped 1104 unrelated white IBD subjects—496 with Crohn's disease, 512 with ulcerative colitis, and 96 with indeterminate colitis from the Cambridge/Eastern (UK) panel—within 760 healthy control subjects for DLG5_113G/A, DLG5_4136C/A, TNF-857C/T, and TNF-1031T/C polymorphisms. Known Crohn's disease-predisposing variants in CARD15/NOD2 were also genotyped to permit analysis for reported epistatic interactions. RESULTS:: TNF-857 was shown to be associated with IBD overall (P = 0.0079). A formal interaction test showed that TNF-857 is associated equally with ulcerative colitis and Crohn's disease. Neither of the DLG5 alleles, however, was associated with IBD (P = 0.32 and 0.35). Subgroup analysis also failed to show evidence of association between either DLG5 allele or genotype frequencies and ulcerative colitis or Crohn's disease. Stratification of TNF-alpha and DLG5 cases by CARD15 genotype made no significant difference in the strength of associations. CONCLUSIONS:: We have confirmed an association between the TNF-857 promoter polymorphism and IBD in a large independent UK dataset but were unable to replicate an association at the previously reported loci within DLG5. This may reflect heterogeneity between the populations, a smaller effect size than originally predicted, or possibly a false-positive result in the original study. Further fine mapping studies of the TNF promoter region and studies assessing functional consequences of TNF promoter polymorphisms are now required in IBD. PMID: 16534418
The multidrug resistance (MDR1) gene encodes for P-glycoprotein, a drug efflux pump. Mice deficient for the MDR1a gene spontaneously develop colitis. In humans, a polymorphism in exon 26 (C3435T) is associated with reduced expression levels and function of MDR1. Currently there are controversial data on the association between MDR1 and inflammatory bowel disease (IBD). The purpose of this study was to examine the involvement of this gene in IBD in a large population of Dutch patients with IBD and family-based controls. Material and methods. A total of 781 IBD cases and 315 controls were investigated. CD phenotypes were determined according to the Vienna Classification. Individuals were genotyped for six single nucleotide polymorphisms (SNPs) close to and in the MDR1 locus. This included the C3435T variant and six microsatellite markers close to and in the MDR1 locus. Single locus association analysis, haplotype association analysis and haplotype sharing statistic (HSS) were used to search for differences between patients and controls. Results. No association was observed for any of the SNPs with IBD as a group, or for ulcerative colitis, Crohn’s disease and Crohn’s disease phenotypes, either by single locus or haplotype association analysis or by HSS. Conclusions. No association was observed between the MDR1 gene and IBD. This suggests that it is unlikely that MDR1 plays a role in IBD susceptibility.


Polymorphisms of the proinflammatory and immunoregulatory cytokines, tumor necrosis factor-alpha (TNF-alpha) and lymphotoxin-alpha (LTA), have been shown to affect their production and be associated with Crohn's disease. However, the actual alleles associated with the disease are variable among populations. The aim of this study was to test whether TNF-alpha and LTA polymorphisms were associated with Crohn's disease in Korean samples. Genotyping for five TNF-alpha promoter polymorphisms (-1031, -863, -857, -308, and -238) and two LTA polymorphisms (intron 1 and Thr60Asn) were performed on 289 Korean patients with Crohn's disease and 399 unrelated healthy controls. Carriers of an individual polymorphism of TNF-alpha at -857T, showed statistically significant association with Crohn's disease (adjusted OR=1.64, 95% CI=1.11-2.41, P=0.013). Following haplotype analysis, carriers of the haplotype consisted of the -1031C, -863A, and -857C alleles showed statistically significant association with Crohn's disease (adjusted OR=1.54, 95% CI=1.02-2.32, P=0.040). Significantly reduced frequencies were seen for the carriers of the LTA Thr60Asn polymorphism in patients (OR=0.62; 95% CI=0.42-0.93, P=0.019), suggesting a protective effect on Crohn's disease. Our data support the hypothesis that the TNF-alpha/LTA genotypes play an important role in the pathogenesis of Crohn's disease in Koreans. PMID: 16931032.


BACKGROUND: Three major polymorphisms of the Caspase-Activation Recruitment Domain containing protein 15 gene have been described to be associated with Crohn's disease. Genotype-phenotype studies reported in literature provide conflicting data on disease localisation and behaviour. We investigated the relation of Caspase-Activation Recruitment Domain containing protein 15 with inflammatory bowel disease and Crohn's disease phenotypic characteristics in a large Dutch cohort and performed a pooled analysis on inflammatory bowel disease patients and Crohn's disease phenotypic characteristics reported in association studies. METHODS: We genotyped 781 cases and 315 controls for the R702W, G908R and 1007fsinsC variants and for six microsatellite markers in and close to Caspase-Activation Recruitment Domain containing protein 15. In the pooled analysis data of 7201 inflammatory bowel disease patients and 3720 controls from 20 studies were included. RESULTS: Association was found for Crohn's disease with R702W and 1007fsinsC, including several disease characteristics, and not for ulcerative colitis. In the pooled analysis all three common Caspase-Activation Recruitment Domain containing protein 15 variants showed strong association with Crohn's disease (p<0.00001; odds ratio varying from 3.0 for single heterozygotes to 14.7 for compound heterozygotes) and not with ulcerative colitis. Phenotype analysis showed association with small bowel involvement, strictureting and penetrating disease. CONCLUSION: Caspase-Activation Recruitment Domain containing protein 15 is associated with Crohn's disease and not with ulcerative colitis. All three common Crohn's disease-associated variants are associated with small bowel involvement, the G908R and 1007fsinsC alleles also being associated with a complicated disease course. PMID: 16920047.
Inflammatory bowel disease genetic research is extremely important to an understanding of primary sclerosing cholangitis (PSC) because PSC is strongly associated with IBD (mostly ulcerative colitis, but sometimes Crohn’s disease).
Recent PSC Literature

by David Rhodes

The following is a brief summary of recent literature on primary sclerosing cholangitis.

Genetics. Wiencke et al. (2006) report that there are no major effects of the CD28/CTLA4/ICOS gene region on susceptibility to primary sclerosing cholangitis in the Norwegian population, although minor effects cannot yet be excluded. Bowlus et al. (2006) conclude that polymorphisms in mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) are not likely to significantly affect PSC susceptibility in the Scandinavian population. In addition, the E/E genotype of the K469E polymorphisms in intercellular adhesion molecule-1 (ICAM-1) does not influence PSC susceptibility in Scandinavia. Melum et al. (2006) report that the 32-base pair deletion of the chemokine receptor 5 gene (CCR5-Delta32) is not associated with either PSC susceptibility or progression in the Scandinavian population. This contrasts with a report from Belgium that the frequency of the CCR5-Delta32 mutation in PSC (6.8%) was significantly lower compared with IBD (12.6%; P = 0.016) and healthy control subjects (12.2%, P = 0.026), suggesting a protective effect of this mutation on PSC (Henkaerts et al., 2006). Interest in the relationship between the CCR5-Delta32 polymorphism and PSC stemmed from the report by Eri et al. (2004) that the CCR5-Delta32 allele frequency was significantly higher in sclerosing cholangitis (17.6%) compared to controls (9.9%, OR 2.47, P = 0.007) and inflammatory bowel disease patients without sclerosing cholangitis (11.3%, OR 1.9, P = 0.027). The CCR5-Delta32 variant was increased in patients with severe liver disease defined by portal hypertension and/or transplantation (45%) compared to those with mild liver disease (21%, OR 3.17, P = 0.03), suggesting that the CCR5-Delta32 mutation may influence disease susceptibility and severity in patients with PSC. Karlson et al. (2006) have observed that genetic polymorphisms in the steroid and xenobiotic receptor (SXR) gene influence survival in primary sclerosing cholangitis. The SXR gene (also known as pregnane X receptor (PXR)) is of particular interest because it has been recently shown to be associated with ulcerative colitis susceptibility.

Mechanisms of cholestasis. Zollner and Trauner (2006) discuss the mechanisms of cholestasis in cholestatic liver diseases. They distinguish between hereditary and acquired forms of cholestasis. Mutations in genes encoding hepato-biliary transport systems can cause hereditary cholestatic syndromes. Exposure to cholestatic agents (drugs, hormones, inflammatory cytokines) can lead to reduced expression and function of hepatic uptake and excretory systems in acquired forms of cholestasis. These authors note that PSC may have an hereditary component: thus, some PSC patients exhibit genetic polymorphisms in genes encoding bile transport proteins such as CFTR and MDR3.

Ursodeoxycholic acid. Beuers (2006) reviews the beneficial effects of ursodeoxycholic acid in various cholestatic liver diseases. In early-stage PBC and PSC, ursodeoxycholic acid protects cholangiocytes against the toxic effects of bile acids. In more advanced cholestasis stimulation of impaired hepatocellular secretion, including stimulation of synthesis, targeting and apical membrane insertion of key transporters, seems to be important.

Fibrates. Japanese researchers continue to report on possible benefits of bezafibrate in improving liver biochemistry in PSC patients (Gondoh et al., 2006; Kita et al., 2006).

Imaging. Jonas et al. (2006) have used a technique called ‘dynamic (99m)Tc-HIDA SPECT’ to assess bile-flow and liver function in patients with PSC. It may become a valuable adjunct to cholangiographic and biochemical findings. An abnormal, hepato-biliary scan liver clearance half-time in patients with PSC correlates to disease duration and increased serum alkaline phosphatase levels, and this variable may be used to identify some subjects with more advanced disease (Arulventhan et al., 2006). Elsajes et al. (2006) note that magnetic resonance cholangiopancreatography (MRCP) is a noninvasive imaging technique that has become very useful for diagnosing primary sclerosing cholangitis. Contrast enhanced magnetic resonance (MR) imaging provides pertinent information of extraductal abnormalities in addition to biliary ductal changes.

Relationship to autoimmune pancreatitis. Mendes et al. (2006) report that a small proportion of PSC patients (9%) have elevated serum IgG4. These patients tend to show more pronounced liver disease, and time to liver transplantation was shorter, suggesting a more severe disease course. This subset of patients behaves similarly to autoimmune pancreatitis patients with biliary strictures, and could potentially respond to corticosteroids. Testing PSC patients for IgG4 and treating those with elevated levels with corticosteroids in clinical trials should be considered (Mendes et al., 2006). Kim et al. (2006) compare autoimmune pancreatitis (AIP) with PSC, and note that whereas AIP patients showed improvement with steroid treatment, most PSC patients showed clinical deterioration. van Buuren et al (2006) describe ‘autoimmune pancreatocholangitis’: an inflammatory-fibrosing disease mimicking pancreatic carcinoma and primary sclerosing cholangitis (PSC). Autoimmune pancreatocholangitis is a distinct inflammatory disorder involving the pancreas and biliary tree. It is not typically associated with IBD and responds to immunosuppressives.

Biliary infections. Kulaksiz et al. (2006) report on the identification of Candida species in the bile from a significant number of PSC patients. Patients with biliary Candida had more severe cholangitis with higher C-reactive protein and serum bilirubin compared to those without Candida infection. In addition to bacterial infection, fungal infection of the bile ducts should also be considered in the treatment of PSC patients (Kulaksiz et al., 2006).

Colon cancer. Rubin and Parekh (2006) observe that risk factors for dysplasia and colorectal cancer (CRC) in inflammatory bowel disease include longer duration of disease, greater extent of disease, younger age at diagnosis, diagnosis with primary sclerosing cholangitis (PSC), family history of CRC, and possibly backwash ileitis and degree of inflammation of the bowel over time. Chemopreventive agents showing promise in preventing CRC include ursodeoxycholic acid (in patients with PSC and ulcerative, aminosalicylates, and possibly statins.

Cholangiocarcinoma. Boberg et al. (2006) report that brush cytology from bile duct strictures in PSC patients is an effective method for detecting cholangiocarcinoma in situ. Similarly, Moff et al. (2006) show that cytopathologic examination of bile duct brushings taken at ERCP may be useful for the early detection of malignant changes in patients with primary sclerosing cholangitis. However, Tischendorff et al. (2006) report that transpapillary cholangioscopy is more sensitive and specific for characterizing

(continued on p. 18)
malignant bile duct stenosis in comparison with endoscopic brush cytology. Malhi and Gores (2006) note that advanced cytological tests of aneuploidy and chromosomal aberrations (e.g. digital image analysis and fluorescent in situ hybridization) aid early diagnosis in high-risk patients.

Workshops. The summary of the NIDDK, Office of Rare Diseases, and Morgan Foundation sponsored research workshop on Primary Sclerosing Cholangitis held in Bethesda, MD in Sept. 2005 was and published in “Hepatology” (LaRusso et al., 2006).

References


Bowlus CL, Karlsen TH, Broome U, Thorsby E, Vatn M; the IBSEN study group; Schrumpf E, Lie BA, Frey Froslie K, Thorsby E, Broome U, Melum E, Karlsen TH, Broome U, Thorsby E, Schrumpf E, Boberg KM, Lie BA 2006 The 32-base pair deletion of the CCR5-Delta32 mutation is strongly associated with primary sclerosing cholangitis in 363 Scandinavian patients with primary sclerosing cholangitis. J. Hepatol. Apr 25 [Epub ahead of print].


