



Working together to provide research, education, and support for people affected by Primary Sclerosing Cholangitis

www.pscpartners.org

PSC Partners Seeking a Cure Newsletter

Vol. 3, Issue 2, November 2007

Edited by David Rhodes and Ricky Safer

PSC Partners Seeking a Cure Board Members:

Dike Ajiri, Lee Bria, Elissa Deitch, Dr. Gregory Everson, Joanne Grieme, Chris Klug, Scott Malat, David Rhodes, Ricky Safer, and Deb Wentz

2008 Conference

The 2008 PSC Partners Seeking a Cure Conference will be held May 2-4, 2008 at the Mayo Clinic in Jacksonville, Florida.

Please consider arriving in Jacksonville on Thursday, May 1, so that you can attend either the St. John's River boat ride (see page 2), or the golf tournament on Friday May 2 (see page 3).

NOVEMBER NEWS

As the Thanksgiving holiday quickly approaches, my thoughts turn to the many reasons why I have been thankful this past year, despite the challenge of living with PSC. I am thankful for every day that I can enjoy with family and friends. I am thankful for all the incredible people that I have gotten to know through PSC Partners Seeking a Cure. The bond that connects all of us provides such wonderful support and encouragement. I am thankful for all the progress that our foundation has made this year, thanks to the combined efforts of so many of our enthusiastic members. We have come a long way in our three years of existence. Thank you to everyone who has helped!

RECENT CONTRIBUTIONS: In the past two months, PSC Partners Seeking a Cure has received two very special contributions. Cordis Corporation, a subsidiary of Johnson and Johnson, has offered us a three year grant of \$9,000 to maintain and enhance our two websites, so that we can reach more PSCers, caregivers, physicians, and researchers worldwide. Dave Rhodes is already busy at work improving our websites. The story behind our second donation is bittersweet. Katy Miller of Creekside, Pennsylvania, a beautiful and talented PSCer, unfortunately passed away on May 7, 2007 of complications of PSC, at the age of 21. In her honor, her family held a golf outing to raise money to help find a cure for PSC. They raised \$7,022 for PSC Partners, and they plan to make this a yearly fundraiser. We all send our condolences to the Miller family, and also our thanks for their help in finding a cure for all of us, so that

In this Issue

- November News p. 1-2
- Summit for Life (Dec 1, 2007) p. 3
- PSC Partners Seeking a Cure Golf Tournament Jacksonville, FL, May 2, 2008 p. 3
- Clever Fundraising p. 4
- Keep Hope in Sight p. 4
- Ways to Help PSC Partners Seeking a Cure this Holiday Season
 - *Notecards* p. 5
 - *Kroger Gift Cards* p. 5
 - *Buy for Charity* p. 6
 - *Search and Give* p. 6
- The Transplant Experience Program p. 6
- Aspen boarder Chris Klug tops podium p. 7
- 2007 PSC Partners Seeking a Cure AASLD Award; Dr. T.H. Karlsen p. 8-9
- Waiting for a Transplant Poem p. 9
- Update on Donations to PSC Partners p. 10-13
- BASL - Dame Shelia Sherlock Research Medal; Dr. B. Eksteen p. 14
- Major genetic breakthrough for ankylosing spondylitis brings treatment hope p. 15-16
- Miscellaneous p. 16

(continued from p. 1)

hopefully, we can prevent similar tragedies in the future. Our thoughts are with the Millers.

MEDICAL SCIENTIFIC ADVISORY COMMITTEE: Our Medical Scientific Advisory Committee has made progress in supporting two important PSC research projects. The STOPSC registry that we are supporting is finally up and running nationally! There are nineteen centers involved in North America. For a list of objectives of the registry, eligibility criteria, and participating centers, please see:

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

In addition, this year we have awarded our first annual prize to the top PSC researcher at the meeting of the American Association for the Study of Liver Diseases (AASLD). On November 3, Dr. Gores (AASLD President) and Dr. Everson (our Medical Advisor) recognized Dr. Tom Karlsen from Norway, who was chosen to receive our award. Dr. Karlsen will also be presenting his PSC research at our 2008 conference in Jacksonville May 2-4, so we will all have the pleasure of meeting him and learning about his very important work. To learn more about Dr. Karlsen's research, please see the article on pages 8-9.

In addition, our Medical Scientific Advisory Committee is making plans for further research projects. As a group, we WILL make a difference and eventually conquer this disease!

SAVE THE DATE: Our fourth annual conference for PSCers and caregivers will be held May 2-4, 2008. Those who have attended past conferences know what an incredibly uplifting experience it is to learn the most updated information about PSC from experts and also to spend time with other PSCers and caregivers, sharing our concerns, experiences, and advice. This year's conference is shaping up well. I'm working closely with Dr. Denise Harnois at the Mayo Clinic, and we hope to have the final weekend agenda ready soon. Our keynote speaker will be Dr. Gregory Gores of the Mayo Clinic in Rochester. Our physician speakers will cover many new topics and will review and update past topics. Thanks to requests in our 2007 post-conference evaluations, we are planning even more casual time to get to know each other.

We are trying a new addition to our weekend plans, and we hope that many of you will be able to join us. If you

can arrive in Jacksonville by Thursday evening, we are planning two great activities for Friday morning/afternoon. For those of you who golf, we are planning a golf tournament, which is shaping up to be a fantastic event. Please see Tim Wholey's article describing this wonderful event. (p 3). Thank you to Joanne Grieme and Tim for planning the tournament. For those of you who don't golf (myself included), we have reserved a boat trip down the St. John's River, which will be a great opportunity to sightsee and to get to visit with each other. Please think about joining us for one of these activities!

As soon as all our conference plans are confirmed, we will post the weekend agenda and the registration forms both on our website (www.pscpartners.org) and on the Yahoo support group. If you have any questions before then, feel free to write to me at

contactus@pscpartners.org

I'm already looking forward to seeing everyone. It is all of you who make the conference weekend so memorable!

2009 CONFERENCE: We are already planning ahead for our 2009 conference. If you might be interested in hosting the 2009 conference in your city, please fill out the form on our website by clicking on "Conferences" and then on "Guidelines for Suggesting Your City as a Location for our 2009 Conference." We need all completed forms returned to us by the January 1, 2008 deadline, so that our Board can make a decision and announce it in Jacksonville. If you are interested or have any questions, feel free to contact me at

contactus@pscpartners.org

Lastly, I'd like to suggest that you think about making a holiday donation of any amount to PSC Partners Seeking a Cure. You might want to join us in our present fundraising campaign, the Road to Jacksonville, which is raising money for more research into the causes and cure for PSC (www.pscpartners.org/RtJ.htm). With everyone's continuing help, we will be able to support more PSC research in the near future!

Happy Thanksgiving!

Ricky Safer

Together in the fight, whatever it takes!

SUMMIT FOR LIFE - DECEMBER 1, 2007

BENEFITING THE CHRIS KLUG FOUNDATION AND THE AMERICAN TRANSPLANT FOUNDATION

Chris Klug, post transplant PSCer and Olympian medal winner in snowboarding, is sponsoring the second annual Summit for Life event on December 1 in Aspen, Colorado in conjunction with the American Transplant Foundation. The purpose for the event is to promote organ donor awareness and celebrate the Gift of Life. Summit for Life is a night time race from the base to the summit of Aspen Mountain - 3,267 vertical feet over 2.5 miles. Racers can use their preferred choice of lighting and non-motorized equipment - snowshoes, skins and other creative means. When racers reach the summit, there will be dinner, refreshments, live music and an awards party. To donate to this wonderful cause, or to learn more about the Summit for Life 2007, please visit

www.SummitForLife.org

or contact Holly at

Holly.Upper@gmail.com.

For more information about the two charities, check out

www.chrisklugfoundation.org and www.AmericanTransplantFoundation.org

Chris would love it if some of our members could participate in this event!

PSC Partners Seeking a Cure Golf Tournament, Jacksonville, FL, May 2, 2008

With just seven months to go before that road ends in Jacksonville, PSC Partners Seeking a Cure is getting ready to hold its very first golf tournament at Windsor Parke Golf Club. After golfers have had their coffee and pastries, they will take to the golf course. At approximately 9:00 AM on the morning of May 2nd, we will kick off with a shotgun start. For those unfamiliar with the shotgun start, groups of 4 golfers will be stationed at different holes around the golf course and a horn will go off signaling the start of play. After 9 holes have been played, a small snack will be provided and golf resumed. After completion, we will have a luncheon with awards and prizes handed out. (Since they play every Wednesday, the doctors will win them all.) Joanne Grieme has secured wonderful prizes from companies supporting our cause. With closest to the hole and longest drive competitions, it would be nice to see if we can raise additional dollars. There will be opportunities for companies to sponsor holes, carts or the refreshment station. So please start thinking about employers or family friends that would be interested in this great opportunity. These are all details that will be worked as the time goes on. We have been able to negotiate a very reasonable fee of \$60 per golfer, which includes continental breakfast, a snack, luncheon, and golf. For those of you interested, please let your family and friends know that they are welcome to join us.

We are expecting to get additional non-conference attendees to participate. We will be able to offer those golfers not coming to the conference the same hotel rate as the attendees. So please encourage your golf buddies to take a vacation in Jacksonville and come support PSC Partners Seeking a Cure by playing along with us. Finally, I would ask anyone who is considering playing to let me know as soon as possible. We would like to get an approximate number of participants. My email address is timwholey@carolina.rr.com

My wife and I look forward to seeing many of you on the course. If we don't see you there, we will see you on Friday night as our road from Denver to Jacksonville is finally realized.

Tim Wholey (Tarheel Tim)

Clever Fundraising!

I recently attended a very clever fundraising event. A friend and her husband have both been closely touched by cancer. She is the former Development Officer for the John Michael Kohler Art Center, a nationally renowned organization located in Sheboygan, WI. She put her development skills to good use and organized her own personal fundraising event.

Guests were invited to a “Wine Tasting to Raise Funds to Fight Cancer”. Each couple was asked to donate \$40 to the American Cancer Society upon entrance to their home. Each couple also brought 2 of the same bottles of wine, one for tasting (tasting sheets and pens provided) and one for a silent auction. Some guests expanded their silent auction bottle selection with a basket – items like a pedicure, selections of pasta and sauces, etc.

The hosts provided a table full of delicious food and offered beer and other beverages for those not interested in drinking wine.

There were 20-25 guests in attendance. It was so much fun comparing different wines and competing with each other for our favorite silent auction bottles and baskets. The guests had a great time...and the hosts raised \$1,500-2,000 for their cause. It made donating enjoyable – a sign of an event worth repeating!

I would challenge everyone to give it a try – how about “Wine/Beer/Chili Tasting to Raise Funds to Cure PSC!”. The entrance donation could be a mile on the Road to Jacksonville, \$50/couple. It’s a very pleasurable evening with friends that helps bring us closer to our goal.

Deb Wentz

Keep Hope in Sight

by Darryl Powlison

Yellow eyes, jaundiced skin,
What a lousy shape I'm in,
Swollen ankles, sloshy belly,
Squishy like they're filled with jelly,
Itch and scratch, til it's sore,
Then I itch and scratch some more,
Cramping legs, cramping feet,
Stretch them out and then repeat,
Sleepy days, up at night,
Thinking isn't quite so bright,
Am I tired or am I lazy?

This itching's going to drive me crazy!

Colors seem to fade to grays,
As I'm feeling more malaise,
But keep a future hope in sight,
When yellow eyes will turn to white,
Fluffy ankles will deflate,
Maybe I won't sleep so late,
Surely I won't feel so drained,
Certainly I'll feel less pained,
Thank you Lord, there's hope in sight,
When yellow eyes will turn to white,
By transplant or Your glory bright.

Ways to Help PSC Partners Seeking a Cure this Holiday Season

Notecards

Please consider using PSC Partners Seeking a Cure Notecards (created by Ali Lingerfelt-Tait) as holiday greeting cards. Notecards can be purchased from by sending a check to:

PSC Partners Seeking a Cure
5237 So. Kenton Way
Englewood, CO 80111

Alternatively, notecards can be ordered on-line via PayPal email: pscpartners@yahoo.com. Please indicate the number of notecards you wish to purchase, and give your name and shipping address. The purchase price of the notecards is dependent upon the number ordered, as follows:

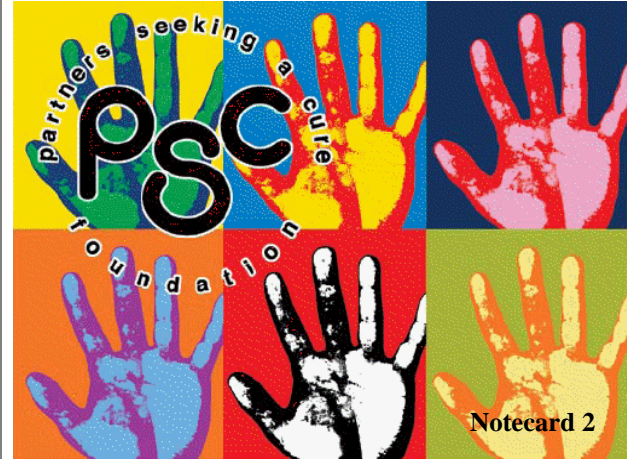
- 1 bundle of 6 cards \$10.00 plus \$1.00 shipping and handling
- 2 bundles (12 cards) \$20.00 plus \$1.75 shipping and handling
- 3 bundles (18 cards) \$30.00 plus \$2.00 shipping and handling

These S&H numbers are for domestic orders only. For international orders please email contactus@pscpartners.org and a shipping quote will be provided. For further details, please see:

www.pscpartners.org/Notecards.htm



Notecard 1



Notecard 2

**Please specify the type of notecard
required (1 or 2).**

Ways to Help PSC Partners Seeking a Cure this Holiday Season

Kroger Gift Cards

A wonderful holiday gift is a Kroger gift card. By purchasing this rechargeable grocery card for \$5, each time it is filled it will be contributing to our foundation. Please explain to the recipient of this card that Kroger will donate \$5 on every \$100 you spend. The card can be filled at the grocery store whenever it is almost empty so that it is ready for the next shopping expedition. The card can be filled at the cash register with either a credit card, check or cash for any amount up to \$500 at a time. The cards are so easy to use and convenient. Once they are filled they can be used just like a credit card. Why not also treat yourself to one? It is a great feeling to know that every time you use it, the PSC Partners foundation will benefit! All of us doing this together will make a big difference.



The Kroger gift cards can be used at the following stores:

- Fred Meyer
- Kroger
- City Market
- Fry's
- CalaBell
- Ralphs
- Dillons
- QFC
- Owen's
- King Soopers
- Smith's
- Baker's
- JayC
- Pay Less

For further details, please visit:

www.pscpartners.org/KrogerGiftCards.htm

Ways to Help PSC Partners Seeking a Cure this Holiday Season

Buy for Charity

If you like shopping online for gifts, then please consider purchasing gifts from “Buy for Charity” and selecting **PSC Partners Seeking a Cure** as the name of your cause:

<http://www.buyforcharity.com/category.asp>

A list of merchants and the percent or \$ amount donations that these stores provide to your selected charity can be found at:

<http://www.buyforcharity.com/allmerchants.asp>

Ways to Help PSC Partners Seeking a Cure this Holiday Season

Search and Give

Search and Give allows you to donate to an organization that has special meaning to you - whether it's supporting your local school or aiding the impoverished. Every day, up to 10 searches will generate a contribution to your selected cause. **PSC Partners Seeking a Cure** is listed as one of these causes/charities.

<http://club.live.com/searchandgive.aspx>

Every Active Supporter Counts

- Search and Give offers an easy way to raise donations for your charity; you just need to sign up and start searching!
- Internet searches done on Search and Give will generate a Microsoft donation to your selected charity.
- Microsoft will make donations on a yearly basis, based on the total tickets contributed to each charity by all participants during that period.

Each supporter can earn a maximum of 10 tickets per day for searches while signed in on Search and Give, and each ticket from those searches will result in a one penny donation by Microsoft.

An unlimited number of additional tickets can be earned by playing a variety of word games and puzzles.

The Transplant Experience Program

Every stage of transplantation is as unique as the individuals experiencing it.

The Transplant Experience Program was created to meet your individual needs at each stage of the transplant process. It's information. It's tools and tips. It's real advice from experts in transplantation, doctors, nurses and other transplant recipients – all designed to help you throughout your transplant experience.

When you enroll in the program you will receive:

- Welcome Kit, including an inspirational video, a personal treatment journal, and a unique pill box to help you organize and carry your medicines.
- Vital information sent directly to you throughout the year – newsletters, emails, videos, special gifts and more
- Regular updates on news and events in the transplant community.
- Shared stories of challenges and successes.
- Tools and advice to help you achieve long-term health.

To join Transplant Experience, visit:

<http://www.transplantexperience.com>

This web site includes frequently asked questions (FAQs) and excellent articles on:

Pre-transplant

- Being Prepared
- Important Questions to Ask Your Transplant Team

Your Experience the First-Year

- Rejection & Its Symptoms
- Anti-rejection Medications
- Staying Healthy

Your Experience Looking Forward

- Long-term Health

Joanne Grieme

Aspen boarder Chris Klug tops podium

Aspen Times, Nov 17, 2007

<http://www.aspentimes.com/article/20071117/SPORTS/111170044>

COPPER MOUNTAIN, Colo. — Chris Klug should consider calling Copper his home mountain from now on.

The Aspen snowboarder gave himself an early birthday present Thursday, besting a field of North America's finest to win Thursday's NorAm giant slalom at the Summit Country resort. The 34-year-old, who turns 35 Sunday, found the podium once more Friday, taking third in the slalom.

He's won seven times at Copper, including twice in November 2005.

"I've had good luck racing there in the past decade," Klug said Friday from Denver. "I've had some great training, I'm dialing it in and feeling strong."

Klug broke his ankle during training in Oregon in August 2006 and struggled to find his stride early last season because of minimal on-snow training. While he never cracked the top 10 on the World Cup circuit, Klug finished strong, winning his seventh and eighth national titles at the U.S. Championships at Alberta's Sunshine Village in late March.

The 2002 Olympic parallel giant slalom bronze medalist is healthy entering this season. It showed in the first of two runs in Thursday's giant slalom - he bested the field by nearly a half-second.

The event was originally scheduled as a PGS, but was changed to a giant slalom late because of scant snow coverage. Softball-sized rocks covered much of Ptarmigan, the typical run used for the NorAm, forcing organizers to change the venue. Klug was hardly fazed; he negotiated a longer course with multiple terrain changes, posting the day's two fastest times.

He beat out friend Jasey Jay Anderson of Canada by one-hundredth of a second in the second run to post a combined time of 1 minute, 37.71 seconds.



Aspen's Chris Klug clears a gate during Friday's NorAm giant slalom at Copper Mountain. Klug finished first, then took third in Friday's slalom. (Courtesy Chris Klug)

"I was telling my coach that, sometimes after you get a good lead on the first run, you kind of ride a little bit safe in the second even though you don't mean to," Klug said. "I was still tops on both runs, so I was happy about that."

Klug said he struggled to find his rhythm on a tight section of eight to 10 gates at the top of the slalom on his first run Friday. He rebounded through the middle and bottom sections and tied for second.

He took third on his second run and wound up with bronze.

"I don't think I had my best day, but to still be on the podium is pretty encouraging," Klug said. "Anybody who's anybody in alpine riding in North America was here, so that's one thing I'm proud of."

Klug finished 11th in the season-opening World Cup parallel slalom Oct. 12 in Landgraaf, Netherlands, then took 18th in parallel giant slalom in Soelden, Austria.

Now, in the early stages of his 17th competitive season, Klug said last season's struggles are behind him. He's finding his stride.

"I had so many struggles. I switched equipment after 15 years, and I broke my ankle. I sort of hobbled into the season," he said. "I got my act together. ... I'm healthy and I still feel like I'm getting better. I'm enjoying it so far, which, for me, is the most important thing."

Klug is slated to spend the next two weeks in the valley. He'll celebrate his birthday and Thanksgiving with friends, train - maybe on his bike instead of his board - then participate in the Summit for Life uphill Dec. 1 on Aspen Mountain.

The World Cup season hits its stride Dec. 8 with two PGS races in Limone Piemonte, Italy. Klug said he wouldn't be surprised if one or two members of a deep, talented American squad reach the podium in Italy.

Will it be him?

"That's the plan," Klug said.

Jon Maletz's e-mail address is jmaletz@aspentimes.com

Congratulations to our "board" member,
Chris Klug!

2007 PSC Partners Seeking a Cure AASLD Award

The recipient of the 2007 PSC Partners Seeking a Cure AASLD Award was Dr. Thomas H. Karlsen (Medical Department and Institute of Immunology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway). Dr. Karlsen received this award because of his outstanding research on the genetic basis of primary sclerosing cholangitis (PSC). Congratulations Dr. Karlsen!

Dr. Karlsen presented the following two abstracts at the 2007 AASLD meeting:

Variation in the MDR3 gene influences disease progression in PSC patients and disease susceptibility in epistatic interaction with a polymorphism in the OST-alpha gene.

E. Melum^{1,2}; K. M. Boberg¹; A. Franke³; A. Bergquist⁴; J. Hampe⁵; S. Schreiber³; B. A. Lie²; E. Schrumpf¹; **T. H. Karlsen**^{1,2}

1. Medical Department, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway.
2. Institute of Immunology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway.
3. Institute for Clinical Molecular Biology, Christian-Albrechts University, Kiel, Germany.
4. Department of Gastroenterology and Hepatology, Karolinska University Hospital, Huddinge, Stockholm, Sweden.
5. 1st Department of Medicine, Christian-Albrechts University, Kiel, Germany.

Background and aims: The multi drug resistance 3 gene (MDR3) on chromosome 7q21 encodes a phospholipid transporter of importance to cholangiocyte membrane integrity and bile solubility (ABCB4; ATP-binding cassette, sub-family B, member 4). Knockout mice of the murine MDR3 analogue (*mdr2*) develop a cholestatic disease resembling primary sclerosing cholangitis (PSC) in humans. The aim of the present study was to investigate the influence of polymorphisms in the MDR3 gene on disease susceptibility and progression in PSC. Genes encoding other transport proteins in the biliary tract were studied simultaneously to evaluate gene-gene interaction (epistasis) on disease susceptibility.

Methods: Single nucleotide polymorphisms (SNPs) covering 10 genes encoding transport proteins for a variety

of bile constituents (MDR3, BSEP, FIC1, MRP2, MRP3, MRP4, ASBT, I-BABP, OST-alpha and OST-beta) were genotyped with SNPlex® technology in 365 Scandinavian PSC patients and 368 healthy controls. Association testing was performed with the Chi-squared test, and epistatic effects were evaluated using logistic regression. Survival was defined as the time from the diagnostic cholangiography to the combined end-point of death or liver transplantation. Effects from genotypes on disease progression were evaluated with Cox regressions.

Results: No associations with PSC susceptibility were seen for any of the individual SNPs. An epistatic interaction between the MDR3 SNP rs8187799 and the OST-alpha SNP rs11185519 affected PSC risk ($p=6.6 \times 10^{-6}$). This effect was robust to correction for multiple comparisons using Bonferroni ($p=0.01$). Two MDR3 SNPs in linkage disequilibrium significantly influenced survival: rs1202283 (AA vs. AG+GG: median 9.8 vs. 14.4 years) and rs4148809 (AA vs. AG+GG: median 9.6 vs. 15.4 years). In Cox regressions, patients homozygous for the A allele at rs1202283 and rs4148809 had an increased risk of death or liver transplantation (hazard ratio (HR)=1.6, $p=0.006$ and HR=1.7, $p=0.002$, respectively). To rule out that this effect was caused by a higher age at diagnosis of PSC or concomitant cholangiocarcinoma, patients with cholangiocarcinoma were excluded and age adjusted Cox regressions were performed, with no change in result (rs1202283 HR=1.7, $p=0.007$ and rs4148809 HR=1.8, $p=0.002$).

Conclusions: Although no associations with any individual SNPs were seen, our present data provide interesting evidence that polymorphisms in the MDR3 gene influence disease progression in PSC patients, and susceptibility to develop PSC in epistatic interaction with a polymorphism in the OST-alpha gene.

HLA association in primary sclerosing cholangitis: detection and finemapping of an HLA independent signal in the complement gene cluster.

T. H. Karlsen^{1,2}; P. Croucher^{3,4}; J. Hampe^{4,5}; A. Franke⁴; E. Schrumpf¹; A. Bergquist⁶; E. Thorsby²; B. A. Lie²; K. M. Boberg¹; S. Schreiber⁴

1. Medical Department, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway.
2. Institute of Immunology, Rikshospitalet-Radiumhospitalet Medical Center, Oslo, Norway.
3. Institute of Medical Informatics and Statistics, Christian-Albrechts-University, Kiel, Germany.

4. Institute for Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany.
5. Department of General Internal Medicine, University Hospital Schleswig-Holstein, Kiel, Germany.
6. Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm, Sweden.

Background: An association between the risk of developing primary sclerosing cholangitis (PSC) and genetic variants within the HLA complex on chromosome 6p21 was detected 25 years ago. This genetic region contains more than 250 closely linked genes, and pinpointing the genetic variants of relevance to PSC has proven extremely difficult. In an attempt to further refine the HLA association in PSC, systematic mapping of the entire HLA complex was performed in a large cohort of Scandinavian PSC patients.

Materials and methods: 365 PSC patients and 368 healthy controls were genotyped for all classical HLA loci (HLA-A, -B, -C, DRB1, DRB3 and DQB1) using a sequencing based approach. A two-stage screen using single nucleotide polymorphism (SNP) markers was subsequently performed. In stage one, 420 SNPs were successfully genotyped with SNPlex® technology. Dissection of the association signals was performed using established statistical packages as well as novel statistical approaches. In stage two, saturation of a distinct risk region using additional 130 SNPs was performed to localize causative variants.

Results: The SNP screen revealed the presence of a wide and complex association signal blurred by a strong-LD haplotype that may harbor several variants strongly associated with PSC, e.g. at HLA-B (odds ratio [OR] HLA-B*08 = 3.5, 95% CI [2.6-4.5], $p < 10^{-16}$) and MICA (OR rs2523495_A = 3.5, 95% CI [2.7, 4.5], $p < 10^{-16}$), which have also been reported in previous studies. When case haplotypes were proactively matched with randomly drawn control haplotypes at markers defining this strong-LD haplotype (i.e. HLA-B*08 and DRB1*0301), a distinct association signal became evident at the complement factor gene cluster within the central HLA class III region. Maximum association in this risk region was observed for a common allele at an intronic SNP (69% vs. 48%, OR=2.5, 95% CI [2.0, 3.1], $p = 10^{-16}$). Interestingly, this allele maps to all known HLA risk haplotypes in PSC (i.e. DR3, DR6 and DR2), while previously reported protective HLA haplotypes in PSC (i.e. DR4, DR7 and DR11) predominantly carry the opposite allele at this position.

Conclusion: The present dataset provides an extensive

insight into the complexity of the HLA association in PSC. Multiple risk variants are likely to exist, some of which have been previously reported in other autoimmune diseases (e.g. at HLA-B and MICA), and others which are PSC-specific. Novel alignment strategies with known risk and non-risk HLA haplotypes in PSC helped to dissect a distinct risk locus for PSC in the central HLA class III region. Ongoing analyses aim to identify the exact susceptibility gene within this region.

For further information on Dr. Karlsen's research on PSC and inflammatory bowel disease, please visit:

<http://www.psc-literature.org/KarlsenT.htm>

Waiting for a Transplant Poem

by Darryl Powlison

Office visits, blood draws, ultrasounds,
X-rays, MRIs, and gaping gowns,
Catscans, cultures, urinalysis,
Hoping to get on the transplant list,
EKGs and an Echocardiogram,
Now I need to get a dental exam!
NPO for ERCPs,
Nulytly for Colonoscopies,
Finally listed – that part's done,
But soon I find it's just begun,
Yellow eyes and itchy skin,
Bulgy tummy, arms so thin,
Blurry thinking, feeling blahs,
Sleeping late and more blood draws,
Feverish rides to emergency,
Family watching late TV,
Waiting for hours just to see,
If they decide to admit me,
Hope the IV goes in right,
Hope I get some sleep tonight,
Hope insurance pays the bills,
Hope I remember all my pills,
Work is harder – no it's me,
Better get on disability,
Up and down the transplant list,
Hope my liver will persist,
Wondering what is coming next,
All the unknowns make one vexed,
But in the end, I know we'll see,
All was to the Lord's glory.

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE (June - November, 2007)

THE ROAD TO JACKSONVILLE FUNDRAISER

DONOR:

Carol and Bruce Grover
Theresa and Andrew Kissel
Karen and Neil Desmond
Barbara and Walter Winding
Jill and Martin Crneckiy Jr.
Alice Senty
Barbara and Jeffrey Ottum
Nancy and Stanley Schreiber
Karen and Hugh Scott
Robert Melzer
Sally and David Oppenheim
Carrie and Michael Draves
Barbara Mueller
Michael Friedman
Rachelle and William Schroeder
Louis Gentine
Susan and Stephen Gould
Joanne and Michael Malin
Peter Steiner
Lisa and Greg Weggeman
Marlene and Carl Kumbalek
Dolores and William Gehrke
Patricia and William Reiss Jr.
Randall Roethel
Elizabeth and Thomas Schueller
Jill and Edward Defrance
Debra and James Riedy
Mary and W. James Grasse
Julia Grandlic
Connie and John Stevens
Kathleen and Richard Wells
Kathie and Robert Norman
Mr. and Mrs. William Hollingsworth
Christine and Steve Johnson
Mary and John D. Crawford
Thorne Family Foundation
R.H. Leverenz
Penny and David Klefstad
Jeannie and Donald Meier
Henry J. Loos
Bruce Mair
Jane and Richard Scott
Mary Lynne Donahue and Timothy Van Akkeren

IN HONOR OF:

Samantha Wentz



The Road to Jacksonville

Traveling from the site of our 2007 conference (Denver, CO), to the site of our 2008 conference (Jacksonville, FL), we have 2,000 miles to cover. Each mile is covered by raising \$50. Our progress is indicated by painting the road **red**.

<http://www.pscpartners.org/RtJ.htm>

Distance Traveled = 438 Miles = \$21,900 Raised for Research, as of 11/17/07

% of Goal Attained = 21.9%, as of 11/17/07

Thank you to all those who have contributed!

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE (June - November, 2007)

THE ROAD TO JACKSONVILLE FUNDRAISER (continued)

DONOR:

Rita Bargerhuff
V.J. and M.K. Baus
Charlene and A.F. Bocchini
Christine and Erich Wilbrecht
Clare and Steven Falconer
Laurence Anne Ruth and Dan Friedman
Jane and Kerry Winans
Peter Bemis
Shirley Kade
Elisa Wierman
Jacqueline and Joel Culp
Jean and Mark Reiner

Lee and Bill Bria
Lynn and Frank Caparaso

Joanne and Stephen Hatchett
Rose Scharfstein
Patricia Merrill

Joanne and Steve Grieme
Diane and Mark Vanderbilt

Judy and David Rhodes

Reggie and Jeff Belmont

Patti and Mike Ross

Lee Bria

Reggie and Jeff Belmont
Lee and Bill Bria
Joanne and Steve Hatchett

Susan and John Crue

Julie and James Terry

Traci Downs
Yvette Matthew
Loryssa and Bradley Howard
Marsha and Daniel Adam

Shelley and Fred Hussey

IN HONOR OF:

Samantha Wentz

Billy Bria

Joey Hatchett

Todd Clouser

Steven Rhodes

Jecy Belmont

Don and Ricky Safer's 40th anniversary

Ricky Safer

Jonathan George's triathlon

Mike Zaloudek

Jared Terry

PSC Partners Seeking a Cure

In honor of Ken Henshaw, Tim Romlein,
Melanie Jett-Scherder and in thankfulness to all the
PSC caregivers, and in memory of PSCers who
have passed on, especially Shauna Saunders

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE (June - November, 2007)

THE ROAD TO JACKSONVILLE FUNDRAISER (continued)

DONOR:

Kathleen and Stephen Barnett
Morley Gwartzman
Nola Gentry and Ned Derhammer
Susan and Terry Egnor
Susan and Scott Malat
Lee and Bill Bria
Bea Maxwell and Naomi Norman
Virginia and Noah Bennett
Diane Taggart
Diane and Charles Tritschler
Marian and William Miller
Nancy and Thomas Clark
Nina Russakoff
Ricky and Don Safer
Ann and Richard Hunt

IN MEMORY OF:

Lauren Boiteau's one year anniversary
Seymour Cherniack

UPDATE ON DONATIONS TO PSC PARTNERS SEEKING A CURE (May - November 2007)

DONOR:

Price, Rosenberg and Bassik, CPAs
Darcy Ward
Katelyn Darna
Terri and John Seeberger
Susan and Robert Laning
Ann and Erik Rhee
Diane and Dwight Devon
Valeria and Dirk Foreman
Judy and David Rhodes
Deanna Webb
Barb and T.J. Henshaw
Nellie Grimes
Rabbi Robert and Lesley Kaplan
Von Welch
Arne Myrabo
Cynthia Rogers

IN HONOR OF:

Susan Malat
Billy Bria
Mike Zaloudek
Luke Foreman
Steven Rhodes
Jesse Fraser
Ken Henshaw's donors
Ken Henshaw
PSC Partners Seeking a Cure
PSC Partners Volunteers

UPDATE ON DONATIONS TO PSCPARTNERS SEEKING A CURE (May - November 2007)

DONOR:

John P. Higdon

Seismic Exchange Inc.
Georgeann and Tim Nicozisin
Pogo Producing Co.
Conway and Charles Adams
John Nicozisin

Cynthia Poulson
Alta and Don Nysted
Joyce Koon
Robin and Thomas Belsha
Stephen Holle

Sima and Cliff Malat

Johnson and Johnson Matching Gift

Davida Nitka
Sharon and Steven Liska
Jo Ann and Louis Scachetti
Jean Ann Strillacci
Franklin School Staff
Aimee and David Lam
Janet and Paul Vignola
Kennedy Elementary School Sunshine Comm.
Electronic Drives and Controls

Ardis and Reverend Ted Althouse

Bill Olmsted

Kathy Miller Memorial Fund
Ricky and Don Safer

IN MEMORY OF:

David K. Mann III

Joe Warmbrodt

Thomas Belsha

Joelle Mazer

James D. Schirmer

Cathy Dent

Mark O. Hettinger

Second anniversary of death of Thomas Rogers

Katy Miller

A BIG THANK YOU TO OUR NEWEST SPONSORS:

Platinum level sponsors:

Carol and Bruce Grover

Copper level sponsors:

Louise Shankland

Gold level sponsors:

Kathy Miller Memorial Fund
Cordis Corporation

Price Rosenberg and Bassik

Silver level sponsors:

Shelley and Fred Hussey

Dr. John Vierling

Bronze level sponsors:

Dr. Bill Olmsted
Barb and T.J. Henshaw
North Fork Foundation
Arne Myrabo

Valeria and Dirk Foreman

Deanna Webb

Jill and Martin Crneckiy

R.H. Leverenz

Kathleen and Stephen Barnett

Copper level sponsors:

Lee and Bill Bria
Reggie and Jeff Belmont

Pogo Producing Company

Sima and Cliff Malat

BASL - Dame Shelia Sherlock Research Medal

<http://www.basl.org.uk/awards.htm>

The BASL Annual meeting is held each year in early September. One of the highlights of the Annual meeting is the presentation of the Dame Shelia Sherlock research prize and lecture. This prize is awarded annually to recognise the enormous contribution of Dame Shelia Sherlock to the development of Hepatology as a discipline in its own right. Furthermore, Dame Shelia was involved in the foundation of the British Liver Club in 1961 which subsequently evolved into The British Association for the Study of the Liver (BASL). She was one of our past presidents and the first recipient of The BASL Distinguished Service Award. In keeping with Dame Shelia's enthusiasm for fostering young researchers, this eponymous research prize is awarded to those without substantive posts in either medicine or science for their research contributions in the field of Hepatology.

2007 Winner of the Dame Shelia Sherlock Research Medal

Dr Bertus Eksteen

Liver Unit - Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust,

Entero-hepatic lymphocyte homing in the pathogenesis of Primary Sclerosing Cholangitis (PSC)

Abstract

A pivotal feature of our immune system is the ability to direct and position immune cells in tissues compartments where they are able to find their cognate antigen and assert their functions(1). For example, lymphocytes that are primed to recognise mucosal antigens are induced to preferentially traffic to the gut by dendritic cells (DCs) in mesenteric lymph nodes and Peyer's Patches. Gut DCs are able to imprint responding T cells with a phenotype which allows them to recognise and respond to gut-specific "address codes". This imprinting is dependent on the unique ability of gut-derived DCs to convert retinol to retinoic acid which in turn allows transcription of gut homing receptors on primed lymphocytes. The gut homing receptors on lymphocytes are the chemokine receptor, CCR9 and the integrin $\alpha 4\beta 7$, which allow the lymphocyte to respond to the gut-restricted chemokine CCL25 and the $\alpha 4\beta 7$ ligand, Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1). Thus the combination of MAdCAM-1 and CCL25 provides a specific gut "address code" to recruit gut-specific lymphocytes to provide immune surveillance and to initiate inflammation(1).

But what occurs if tissue specificity is lost or if molecules such as MAdCAM-1 and CCL25 are aberrantly expressed? In such a scenario mucosal lymphocytes could potentially be recruited to extra-intestinal sites and cause inflammation outside the gut(2). Extra-intestinal inflammation is often seen in patients suffering from inflammatory bowel disease (IBD) and can generally be divided into diseases which occur either at the same time as flares of bowel inflammation (joint, skin and eye disease) or those that run a course that is independent of inflammation in the bowel (liver disease). It is possible that concurrent extra-intestinal diseases occur as a consequence of inflammatory cytokine release from the inflamed gut but such a mechanism would not explain extra-intestinal liver disease, such as autoimmune hepatitis and primary sclerosing cholangitis (PSC) that develop when bowel inflammation is quiescent or after the bowel has been removed.

Hence, it has been our hypothesis that extra-intestinal liver disease in IBD might be explained by aberrant homing of gut lymphocytes to the liver and is the main focus of my research(3).

Our lab had previously shown that PSC is associated with aberrant expression of MAdCAM-1 on hepatic endothelium(4) and in my research I have gone on to show that PSC is associated with the recruitment of long-lived mucosal memory T-cells in response to the aberrant expression of MAdCAM-1 and the gut-specific chemokine CCL25(5). CCL25 was only detected in significant amounts in liver tissue from patients with PSC and this aberrant expression results in the recruitment of mucosal T cells expressing $\alpha 4\beta 7$ and CCR9. I was able to show that these cells are memory cells that secrete high levels of IFN γ on stimulation suggesting that they could trigger chronic inflammation when recruited to the liver(5). Although CCR9+ $\alpha 4\beta 7$ + lymphocytes isolated from PSC livers had a phenotype that is identical to mucosal T cells it was still plausible that these lymphocytes had not originated in the gut but had been primed in the hepatic lymph nodes by hepatic DCs that induced aberrant expression of adhesion molecules. This led me to determine whether DCs isolated from the liver of patients with PSC have the ability to induce the gut homing phenotype in responding T and B lymphocytes. Liver DCs were competent in inducing activation and proliferation but were not able to induce a gut-homing phenotype in the absence of exogenous retinoic acid. Thus, confirming the mucosal origins of the $\alpha 4\beta 7$ /CCR9+ cells in the liver(6) (and work in preparation).

Only 20% of infiltrating T cells in PSC are $\alpha 4\beta 7$ /CCR9+ and thus of mucosal origin but their ability to secrete IFN γ allows them to induce the local expression of the chemokines CXCL9-11. In collaboration with Stuart Curbishley in our lab I have shown that the sustained expression of these chemokines by hepatic endothelium leads to the recruitment of further effector lymphocytes expressing the receptor CXCR3(7). Thus the inflammatory response can be broadened and sustained leading to chronic persistent inflammation and liver damage. Once recruited to the liver effector cells must be positioned in tissues and I have shown that another chemokine receptor, CCR10, is involved in the positioning of mucosal T cells at the biliary epithelium in PSC(8). I was able to show that the ligand for CCR10, CCL28 is secreted by cholangiocytes in response to IL-1 β and LPS stimulation and that this chemokine activates the adhesion of CCR10 expressing intrahepatic T cells to VCAM-1 expressed by inflamed cholangiocytes. This interaction is mediated by another integrin $\alpha 4\beta 1$ which I have shown not only provides a localisation signal for effector T cells at the biliary epithelium but also provides a potent NF κ B dependent survival signal to keep these effector cells alive and thereby to promote the persistence of inflammation.

Thus I propose a novel hypothesis to explain the extra-intestinal complications of inflammatory bowel disease in which long-lived mucosal memory T cells undergo entero-hepatic recirculation between the liver and gut resulting in hepatitis and liver injury.

1 W. W. Agace, Nat. Rev. Immunol. 6, 682 (2006). 2 A. J. Grant et al., Lancet 359, 150 (2002). 3 D. H. Adams, B. Eksteen, Nat. Rev. Immunol. 6, 244 (2006). 4 A.J. Grant et al., Hepatology 33, 1065 (2001). 5 B. Eksteen et al., J. Exp. Med. 200, 1511 (2004). 6 J. R. Mora et al., Science 314, 1157 (2006). 7 S.M. Curbishley et al., Am J Pathol. 167, 887 (2005). 8 B. Eksteen et al., J. Immunol. 177, 593 (2006).

Major genetic breakthrough for ankylosing spondylitis brings treatment hope

18:00 Sunday 21 October 2007

http://www.wellcome.ac.uk/doc_WTX041500.html

Research funded by the Wellcome Trust and the Arthritis Research Campaign has identified two genes implicated in the disease ankylosing spondylitis, a common disease causing primarily back pain and progressive stiffness. The research, published online today in 'Nature Genetics', suggests that a treatment currently being trialled for Crohn's disease may also be applied to this disease.

Ankylosing spondylitis affects as many as 1 in 200 men and 1 in 500 women in the UK, typically striking people in their late teens and 20s. While it mainly affects the spine, it can also affect other joints, tendons and ligaments. More rarely, it can affect other areas, such as the eyes, lungs, bowel and heart. ¹ High-profile sufferers of the condition include former England cricket captain Mike Atherton.

Now, using a technique known as genome-wide association scanning, researchers led by Professors Lon Cardon, Matthew Brown and Paul Wordsworth from the Wellcome Trust Centre for Human Genetics at the University of Oxford, and Dr Panos Deloukas from the Wellcome Trust Sanger Institute, Cambridge, have analysed DNA samples from 1000 patients with ankylosing spondylitis and a further 1500 people unaffected by the disease in search of genetic mutations which, if present, increase a person's risk of developing the disease. The findings from this study were then confirmed by a team at University of Texas (Houston) led by Professor John Reveille.

"Ankylosing spondylitis is a painful and often very disabling disease," says Professor Brown. "Yet, our understanding of the causes of the disease, and hence our ability to treat it effectively, is relatively poor."

The researchers have identified two genes, ARTS1 and IL23R, which increase the risk of developing the disease. Together with the genetic variant HLA-B27, this takes the number of genes definitely known to be involved in the disease to three. A person carrying all three variants would be expected to have a one in four chance of developing the disease.

The IL23R gene plays a role in the immune response to infection, providing instructions for making a receptor present on the surface of several types of immune system

cells. The receptor is involved in triggering certain chemical signals inside the cell that promote inflammation and help coordinate the immune system's response to infection. It is already recognised as playing a role in a number of autoimmune diseases, such as Crohn's disease (a type of inflammatory bowel disease) and psoriasis (a skin disease). Ankylosing spondylitis, Crohn's disease and psoriasis were known to often occur together, and this genetic finding goes a long way to explain why.

Professor Brown believes that the unexpected involvement of IL23R in ankylosing spondylitis provides a major step towards being able to treat the disease.

"We already know that IL23R is involved in inflammation, but no one had ever thought it was involved in ankylosing spondylitis," says Professor Brown. "A treatment for Crohn's disease that inhibits the activity of this gene is already undergoing human trials. This looks very promising as a potential treatment for ankylosing spondylitis."

Scientists have known that there is a genetic component to ankylosing spondylitis for 37 years, since the discovery of the gene HLA-B27. However, how this gene led to disease is not known. Professor Brown believes that the gene ARTS1 may hold the answer.

A protein created by the HLA-B27 gene takes fragments of pathogens and displays them on the outside of immune cells. These fragments then trigger the immune system to fight against the pathogen. ARTS1 is involved in breaking up the pathogen into 'bite-size chunks' that can be displayed by HLA-B27.

"This strongly suggests that in ankylosing spondylitis, there are problems with the information that the HLA-B27 protein receives, thereby causing the disease," says Professor Brown.

Scientists believe that ankylosing spondylitis may be triggered in genetically susceptible people by bacteria commonly found in the gut. Why this should be the case is unclear, but it is hoped that the new genetic discoveries will help answer this question.

"These findings are very exciting and show the value of exploring the genetics of disease," says Dr Mark Walport, Director of the Wellcome Trust. "It usually takes many years between genetic discoveries and new treatments for disease. In this case the two genes discovered to be associated with ankylosing spondylitis provide

(continued from p. 15)

striking insights into the mechanisms of the disease and offer a possible new pathway for treatment."

The study is a collaboration between the Wellcome Trust Case Control Consortium and the Australo-Anglo-American Spondylitis Consortium funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

"These genetic studies involve large patient samples and require expertise over a wide range of scientific specialities", says Professor Cardon. "Bringing together these two consortia was the final key that enabled these exciting discoveries."

Recruitment and collection of samples of patients with ankylosing spondylitis was assisted by the National Ankylosing Spondylitis Society.

Contact

Craig Brierley
Media Officer
Wellcome Trust
T +44 (0)20 7611 7329
E c.brierley@wellcome.ac.uk

Notes for editors

1. Statistics according to National Ankylosing Spondylitis Society.
2. Wellcome Trust Case Control Consortium. Association scan of 14 500 nonsynonymous SNPs in four diseases identifies autoimmunity variants; 'Nature Genetics', published in advance online 21 October 2007.
3. The Wellcome Trust is the largest charity in the UK. It funds innovative biomedical research, in the UK and internationally, spending around £500 million each year to support the brightest scientists with the best ideas. The Wellcome Trust supports public debate about biomedical research and its impact on health and wellbeing. The Wellcome Trust Case Control Consortium was supported by: the Medical Research Council; the British Heart Foundation; the Juvenile Diabetes Research Foundation; Diabetes UK; the Arthritis Research Campaign; the National Association for Colitis and Crohn's Disease; and MDF The Bipolar Organisation.
4. The Arthritis Research Campaign is the fourth largest medical research charity in the UK, raising more than £30 million in 2006/7 entirely from public donations. It currently funds more than 350 research projects into all types of arthritis and musculoskeletal conditions in medical schools and hospitals around the UK, and also has an extensive educational remit.

Additional Contact Information

Ricky Safer is the principal contact person for our PSC Partners Seeking a Cure Foundation. She can be reached at: contactus@pscpartners.org

Submitting Newsletter Articles

If you would like to contribute an article to a future issue of this Newsletter, please e-mail it to: newsletter@pscpartners.org

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>) 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.

We offer several levels of sponsorship

- Platinum level: \$10,000
- Gold level: \$5,000
- Silver level: \$2,500
- Bronze level: \$1,000
- Copper level: \$500

Thank you for your generosity!

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."



GiveLife

Note to Readers

Articles in this newsletter have been written by persons without formal medical training. Therefore, the information in this newsletter is not intended nor implied to be a substitute for professional medical advice. Please consult with your doctor before using any information presented here for treatment. Nothing contained in this newsletter is intended to be for medical diagnosis or treatment. The views and opinions expressed in the newsletter are not intended to endorse any product or procedure.