Welcome to the Summer 2010 Edition of the UCSF Lupus and RA Genetics Research Projects Newsletter!

First and foremost, we wish to thank you and your family for taking time to provide us with valuable questionnaires and DNA samples. This year, we have exciting new discoveries to report. With your help, we have made significant advances in understanding the genes associated with the development of lupus and rheumatoid arthritis, and those related to particular symptoms. Here are some highlights:

- Identification of genetic markers for patients with severe lupus
- Understanding and improving treatment for lupus patients with arthritis
- Investigations in Sjögren’s Syndrome, and how it affects RA and lupus patients

The ongoing support of our study participants and continuing advances in technology have allowed us to deepen our study of genetic and other environmental risk factors for the development of lupus and RA. We are optimistic that one day the knowledge gained from this study will facilitate the development of new therapies to better treat lupus and RA patients, and possibly prevent these diseases for future generations.

Meet the Lupus and RA Genetics Research Team

From Top Row (left to right): Lindsey Criswell MD MPH, Sharon Chung MD MAS, Kirsten Sterba, Ruby Harrison, Joanne Nititham, Rachel Kaiser MD MPH, Kim Taylor PhD MPH, Guada Respicio MD, Kimberly Ho, Ilana Richman MD, Jessica Wolf, Arundathi Malladi MD (Not Pictured: Jennifer Barton MD and Clare Cleveland).
The Lupus and RA Genetics Research Projects and Collaborating Studies

Healthy Mothers for Mother-Child Study: In collaboration with Blood Centers of the Pacific in San Francisco, CA, Central Blood Banks in Pittsburgh, PA, and with help from our Mother-Child Study participants, we have expanded enrollment to include healthy mothers who do not have an autoimmune disease. They serve as our comparison group, which allows researchers to better understand how the immune system works.

To our Mother-Child Study Participants: Help Us Enroll More Healthy Mothers!

Last year, you should have received an information packet to forward to a fellow mother who may be interested in helping out with the study. If you have already shared our information with her, thank you! If you would like to refer someone else to the study, please do not hesitate to contact us again.

If you have not shared our information with anyone yet, it is not too late! Similar to yours, her enrollment will take place entirely by mail. We will ask her and one or more of her biological child(ren) (age 7 or older) to provide small saliva samples. Mothers of all ages are eligible. Consider asking your friends, neighbors, and co-workers to join in our research.

For more information, or to refer a health mother to the Mother-Child Study, call us toll-free 1 (888) 223-3067 x3.

Genes are Associated with Autoantibody Production in Lupus
Sharon Chung, MD MAS

Lupus patients commonly develop antibodies to specific parts of their own body’s cells, such as the cell nucleus, certain cell proteins, and cell membranes. These antibodies, called autoantibodies, are associated with developing lupus-related kidney disease, blood clots, and certain types of skin rashes.

Autoantibodies that recognize double-stranded DNA (dsDNA), the type of DNA found in human cells, are particularly important in lupus. This autoantibody is found in about half of lupus patients and can trigger lupus-related kidney disease. In addition, patients with these autoantibodies are more likely to have more severe lupus. Therefore, Dr. Sharon Chung, a junior faculty member in our research group has been conducting research to identify genetic risk factors associated with producing this autoantibody.

In our most recent study, we examined over 400,000 genetic markers across the genome in approximately 1700 lupus patients and 4800 healthy control individuals to identify genes that were associated with anti-dsDNA autoantibody production. We found that many genes previously identified as lupus (cont. on page 3)
A Conversation with Kim Taylor, PhD MPH

Kim Taylor is the lead statistician on our team, and when she is not busy conducting a variety of complex statistical genetic analyses for The Lupus and RA Genetics Projects, she is usually spending time with her two adorable children and incredibly supportive husband, playing piano, enjoying being with friends, teaching aerobics, or jogging with her dogs.

Q: What are the general activities of the “data team” and how would you describe your role in our research group?
Kim Taylor: “We deal with the end result. After all the initial work of recruiting patients, requesting and reviewing medical records, collecting samples, and lab work is done, the “data team” is responsible for storing, organizing, and managing the data that is produced at each of these steps. My role in the team is to take this data and determine whether or not the associations between the clinical information (derived from patient questionnaires and medical records) and the genes (collected though saliva and blood) are indeed real correlations or due to random chance. That’s what statistics is all about in epidemiologic research.”

Q: Why is it important to have a statistician as part of a research team?
Kim Taylor: “A statistician specializes in distinguishing between “real” associations vs. random chance relationships and therefore can increase the accuracy and confidence in the research findings. One way of doing this is by comparing the genes of Lupus or RA patients to those of healthy individuals. The larger the sample size and the more people that participate in research (especially genetic studies), the clearer these answers become.”

Q: What special tools do you use as part of your job and what sorts of challenges do they pose?
Kim Taylor: “There is special computer software used for statistical analysis and even more specialized software for doing genetic analysis. The challenge is that genetics is a rapidly evolving field and the tools used to study them change just as fast. Staying on top of the current tools and methods is very important.”

Q: Please describe your prior work background, and why you chose to work with The Lupus/RA Genetics Project?
Kim Taylor: “My background is in computer science and I used to work as a software engineer. I found my work in software engineering to be unfulfilling and I knew in my heart that I wanted to do something more meaningful to me. Health and medicine have always intrigued me – particularly both genetics and autoimmunity – so I decided to pursue a Master’s Degree in Public Health, with an emphasis in epidemiology (the study of disease origin and spread), at UC Berkeley. Working as a statistician with The Lupus and RA Genetics Project has allowed me to utilize my computer programming skills in a context that is much more fascinating to me. I am thrilled at how it all worked out.”

(cont. from page 2) susceptibility genes were also associated with anti-dsDNA autoantibody production. Interestingly, we found that many previously identified lupus susceptibility genes were more strongly associated with anti-dsDNA autoantibody production than with lupus itself. These findings suggest that these genes have a greater role in developing this autoantibody than in developing lupus.

Our study indicates that having certain genetic markers predisposes lupus patients to develop this autoantibody, and thus may predispose lupus patients to develop more severe disease. Identifying these genes and understanding their role in autoantibody production may provide new targets for therapies to control autoantibody production and organ damage in lupus in the future.

The Lupus Sister Research Study- www.sissle.org

Following sisters of SLE patients may shed light on risk factors and disease progression

We are very excited to tell you about a new national study that is likely to lead to a better understanding of how and why lupus develops in some women, and not in others. The SisSLE study is designed to answer these questions, with the hope that the answers will lead to preventive treatments even before lupus develops.

In order to get these answers, they need to enroll unaffected sisters of lupus patients and follow them for five years, with telephone interviews every six months, and blood draws only once a year. This will allow them to detect changes in the immune system, and also check for evidence of some environmental exposures that may trigger the development of lupus.

This project is being led by our collaborators at the Feinstein Institute for Medical Research in New York. To learn more, please visit the study website at www.sissle.org, call 1(877) 698-9467, or simply call us at UCSF toll-free, 1(888) 223-3067 x1. Lupus researchers nationwide are joining together for this project, but in the end success depends on sisters helping sisters to understand and prevent lupus.
Dry Eyes and Dry Mouth: Could you have Sjögren’s Syndrome?  
Arundathi Malladi, MD

Sjögren’s Syndrome is an autoimmune disease that primarily affects the salivary and tear glands causing severe dry eyes and dry mouth symptoms. While a patient may have Sjögren’s Syndrome (SS) on its own, many RA and SLE patients also develop SS. The presence of both SS and either RA or SLE is called secondary SS. Up to 20% of patients with SLE and 30% of patients with RA may eventually develop secondary SS.

A diagnosis of SS is made based on a combination of symptoms, blood test results and specific tests involving the eyes and salivary glands. Patients diagnosed with SS require careful care from a dentist and ophthalmologist, and often also from a rheumatologist. Aside from dry eyes and dry mouth symptoms, SS can cause a number of other problems including fatigue and arthritis. Most importantly, patients with SS have been shown to have an increased risk of developing lymphoma.

Our knowledge about the causes and treatments for SS is limited at this time. Researchers at UCSF are part of an international network that is studying this important autoimmune disease. This project is called the Sjögren’s International Collaborative Clinical Alliance, or SICCA (http://sicca.ucsf.edu/). If you have dry eyes or dry mouth symptoms, you may be eligible to participate in this study and receive comprehensive clinical and laboratory examinations to determine whether you have SS. By participating, you will be part of an international effort to support future research projects on the causes, treatment and prevention of SS through provision of clinical data and bio-specimens.

For more information and to find out if you are eligible for the SICCA project, please call Danielle, the Research Coordinator at UCSF, at 415-476-0535.

Blood Samples are Very Important for Our Research

Blood provides 2-3 times more DNA than saliva

If you are a lupus or RA patient willing to donate a small blood sample (and have not already done so), please contact us toll free at

1 (888) 223-3067 x1, to request a blood kit.

- There will be no cost to you
- You can live anywhere in the USA
- A $25 check will be mailed to you as a thank-you for your time an effort

Arthritis in Lupus
Guada Respicio, MD

Systemic lupus erythematosus (SLE or lupus) is a chronic autoimmune condition that has varied clinical and laboratory manifestations. Joint involvement is the most frequent manifestation of SLE, frequently present at the time of diagnosis, appearing either as joint pain (arthralgia) or joint inflammation (arthritis). Joint involvement in lupus typically affects two or more joints and is characterized by pain, swelling, or tenderness. Unlike the arthritis that characterizes rheumatoid arthritis, arthritis in lupus generally does not lead to permanent damage or deformity.

Lupus disproportionately affects women and has a less favorable outcome among minority population groups, including African-Americans, Hispanics, and Asian-Americans. Whether these differences are due primarily to socioeconomic factors among individuals from ethnic minority groups or to biologic or genetic differences remains unclear.

Consistent with some prior reports, Dr. Guada Respicio, a rheumatology fellow working on the Lupus Genetics Project, has observed that a subset of lupus patients in her clinic have developed severe arthritis that is refractory to common forms of arthritis treatment. Thus, she sought to study the frequency of arthritis among our ethnically diverse lupus cohort and to determine whether specific ethnic, clinical or laboratory factors are associated with this disease subtype.

Preliminary results from her study reveal that 69% of the lupus patients in our collection have arthritis. The frequency of arthritis is higher among Hispanics (74%) and African-Americans (75%) and lower among Asians/Pacific Islanders (59%). Indeed, Asian/Pacific Islander ancestry appears to protect against the development of arthritis. Furthermore, consistent with other studies of ethnically diverse populations we found that Caucasian lupus patients tend to have less kidney involvement and more skin involvement; African-Americans have increased skin involvement (often presenting as discoid rash, which leads to scarring), as well as a higher likelihood of developing kidney involvement; and Hispanics and Asians also tend to have more kidney involvement. We did not find any specific laboratory finding that indicates an increased likelihood of developing arthritis in lupus, however Dr. Respicio also plans to study specific gene variants that may increase the risk of developing arthritis in lupus.

These preliminary results highlight differences in the development of arthritis among lupus patients from different ethnic groups, underscoring the variable expression of this disease. Eventually we hope to identify specific genes or other biologic factors that explain these differences in arthritis in lupus. This information will be important for the interpretation of genetic studies in lupus and for the development of therapeutic strategies that target specific disease manifestations.
The Recruiter Experience
Kimberly Ho, Jessica Wolf, and Ruby Harrison

Since our enrollment process can be completed entirely by phone and/or through the mail, we don’t have the opportunity to meet every single one of the participants in our research studies. Fortunately, when we visit our local rheumatology clinics (such as UCSF, San Francisco General Hospital and Highland Hospital in Oakland) we can complete a patient’s enrollment entirely in person. In-person enrollment is great because it eliminates the need to wait for samples and paperwork to arrive by mail, and, more importantly, it allows us to connect with each patient’s situation.

As most of our patients know, and as we have learned at our clinic visits, each person’s experience with autoimmune disease is unique. Some patients we meet are doing well, while others are struggling with their symptoms. We especially appreciate the patients who are not feeling well but who are still willing to speak with us because it is important to have a diverse representation of disease severity. There may be different genetic factors that play a role in disease activity or severity and we want to try and identify what these factors might be.

Having many different ethnic groups represented in this kind of study is vitally important to knowing why lupus and RA occur more frequently in certain ethnic populations. The San Francisco Bay Area is a very diverse community, and being able to recruit here has been invaluable for our research.

Although patients understand there is no direct benefit to them, they tell us they participate because they want to increase awareness or advance knowledge that may lead to better treatments for lupus and RA. With that motivation in mind, we look forward to continuing our clinic recruitment efforts. To all the patients and their family members who have selflessly given their time and energy to our research studies, as well as the doctors (see interview with Dr. Gross below), nurses, and clinic staff members we continue to work with this year, we would like to express our deepest thanks. We wouldn’t be able to do any of this without you.

An Interview with Andrew Gross, MD

Dr. Gross joined UCSF in 2003 and was recently appointed director of the UCSF Arthritis Clinic. He not only serves as a team leader, he also manages his own patients’ care, and supervises basic science research. Outside of his career, Dr. Gross loves being a husband and father to his amazing wife and three young children (ages 10, 9, and 2). He makes time to play soccer, bike, and ski with them.

Q: As UCSF’s new rheumatology clinic director, how do you envision the future direction of the clinic, particularly in providing patients opportunities to take part in research?

Dr. Gross: “Joined by my colleagues, we seek to continue to improve the capacity of our clinic to see new patients through both statewide and nationwide referrals. The ability to provide outstanding care, even for the most complicated rheumatologic cases, is supported by the presence of highly experienced clinicians. My background is in basic science research, and I remain engaged in these investigations in hopes of better understanding the mechanisms of autoimmune diseases, like lupus and rheumatoid arthritis. In addition to my own research, I remain strongly committed to developing other research efforts within the UCSF rheumatology program.”

Q: What was your previous position like and how has that influenced your role as director?

Dr. Gross: “I received my medical degree and training at Tufts University and at Tufts-New England Medical Center. There I engaged in research looking specifically at the relationship between the Epstein Bar virus and lupus. When I came to UCSF, I further developed my understanding of immunology and B-cell biology (the cells that make antibodies) to better understand lupus. These experiences not only enriched my interest to continue to study mechanisms of disease, they also taught me how to manage multiple projects at once, and they developed my skills as a team leader. Each has served me well as I have taken over as clinical director.”

Q: What are your views on “bench to bedside,” in relation to this clinic?

Dr. Gross: “This is a huge interest of mine; in fact, it’s what we are doing right now. These terms relate to the idea of using patient samples from the clinic, studying them in the lab, and with the newly gained knowledge, find ways to better treat and help these patients (it really should be called “bedside to bench to bedside”). We are currently engaged in a grant supported project to study B-cell function in lupus. We are enthusiastic about this because it attempts to better understand the reasons why people develop lupus. It may also provide us with new insights into ways to categorize patients with lupus based on immunologic characteristics. This information could prove useful when trying to develop better therapies for this difficult to treat disease. I am not only eager to pursue my own research interests, but also thrilled to support a variety of related research projects through the clinic.”
Getting Greener!

Hundreds of participants have already signed up—thank you!

To receive Email notices when our yearly newsletter is available,
Simply visit our website http://medicine.ucsf.edu/lupus

Click on Newsletters, and follow the instructions under GO GREEN!

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San Francisco, CA 94143-0500

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Keep In Touch!

We want to be able to share future research updates and important news with you about the studies you and your family members are enrolled in. Please call us if:

• Your address or phone number has changed
• You need replacement saliva or blood kits
• You or your family members have developed a new autoimmune disease

Call us toll free at:
1 (888) 223-3067 x 1
Or visit our website:
http://medicine.ucsf.edu/lupus

Thank you for your participation in this important research!