Welcome to the Spring 2009 Edition of the UCSF Autoimmune Disease Genetics Research Projects Newsletter!

In this issue we report on exciting advances in rheumatoid arthritis and lupus research. Your participation in the UCSF Autoimmune Disease Genetics Research Projects has made all of this research possible. With your help we have made significant advances in understanding genetic risk factors for rheumatoid arthritis and lupus, as well as investigation into treatment and care of rheumatoid arthritis patients. Here are some highlights of recent research showcased in this newsletter:

- Identification of risk factors for blood clots in lupus patients
- Discovery of additional lupus and rheumatoid arthritis susceptibility genes
- Understanding and improving treatment for patients with rheumatoid arthritis
- Investigations into the interplay of ancestry, environment, and lupus symptoms or outcomes

Your participation in conjunction with recent advances in bioinformatics and genomics technology makes it possible for us to continue to discover genes and other environmental risk factors for autoimmune diseases.

We thank you and your family for taking time to provide us with valuable questionnaires and DNA samples.

UCSF Autoimmune Disease Genetics Research Group

Inside This Issue:

Blood clots and lupus.........................2
RA research in the Netherlands..........2
Study participation chart..................3
Genes, environment, and lupus........3
Advancing treatment of RA..............4
Genome screens for lupus risk genes....4
Recruitment at Highland Hospital......5
Your heritage and lupus symptoms.....5
Two new risk factors for lupus and RA..5
Keep in touch and Go Green!..........6

Top Row (left to right): Joanne Nititham, Sharon Chung MD MAS, Ruby Harrison, Clare Cleveland, Rachel Kaiser MD MPH, Jennifer Barton MD, Elisabeth Greer PhD, Lindsey Criswell MD MPH. Bottom Row (left to right): Jessica Wolf, Kimberly Ho, Dorthy Lee, Kim Taylor PhD MPH. Not Pictured: Ilana Richman, UCSF medical student.
Our research group collaborates with the Genetic Epidemiology Unit at Erasmus Medical Center (EMC) in Rotterdam, Netherlands. Dr. Lindsey Criswell first fostered this collaboration when she spent a year researching abroad in the Netherlands. Our research focuses on an isolated population in Rucphen, a small region in the Netherlands. The genetic similarity of the individuals in this region will make it easier to identify genes that may contribute to the development of rheumatoid arthritis (RA). This population has already proved helpful in identifying genes involved in Parkinson’s disease, multiple sclerosis, and other complex diseases. In fact, a recent study of this population published in Nature Genetics uncovered the first neuronal gene implicated in susceptibility to multiple sclerosis (an autoimmune disease affecting the nervous system).

With the help of Professor Hazes, head of rheumatology at EMC, Dr. Hans van Groenendael, a rheumatologist caring for the majority of patients in the population, and study coordinator Petra Veraart we have enrolled over 200 individuals in the study. We can analyze genetic markers in these individuals, hopefully identifying unique genes involved in RA. Studying the genetics of this isolated population provides a complementary approach to other studies currently underway in our group. Together this research will help us identify disease susceptibility genes and possible therapeutic targets.

Lupus can cause arthritis, rashes, kidney damage, and blood clots (called “thromboses”) such as strokes or clots in the lungs (also called a “pulmonary embolism”). Patients with lupus experience blood clots more often and at a younger age than people without lupus. Such clots can have devastating consequences including paralysis from a stroke, recurrent miscarriages, and even early death. Treatment sometimes requires life-long medication with warfarin (commonly known as a “blood thinner”). This treatment itself carries the risk of bleeding. Clearly, we need to improve our ability to identify which lupus patients are at greatest risk for having a blood clot.

We know of several risk factors already. For example, certain positive blood tests tend to be found in lupus patients who experience blood clots. These tests look for antibodies called “anti-phospholipid antibodies”. However, not all lupus patients with thrombosis have these positive blood tests and not all patients with these positive blood tests have a blood clot. As our best clue, therefore, it is still imperfect. Our research group is studying patients enrolled in the UCSF Lupus Genetics Project to better understand contributing factors to thrombosis.

In a recent study, we demonstrated that mutations in the Factor V gene double the risk for thrombosis in lupus patients. Factor V is a gene that contributes to thrombosis in the general population. Factor V plays a role in blood clotting and the Factor V Leiden mutation increases your risk for thrombosis (this mutation is found in 5-7% of Caucasians). Understanding the increased risk for thrombosis in patients with lupus and the Factor V Leiden mutation will lead to improved identification of lupus patients at risk for thrombosis.

In another study we presented at a recent American College of Rheumatology meeting, we found that smoking, older age at lupus diagnosis, lupus kidney involvement, having taken strong lupus medications such as Cytoxan, and having had lupus for many years increased a lupus patient’s risk of having a blood clot. Many of these findings, such as the strong medication use, having had lupus for a long time, and having kidney involvement, may just suggest that patients with more severe lupus are at higher risk for having a blood clot, not that these medications themselves cause a blood clot. Therefore, patients should not avoid these potentially life-saving medications because they are associated with higher rates of thrombosis. Rather, this suggests to physicians that we need to aggressively manage lupus patients with such severe disease manifestations.

However, at least one of these risk factors – smoking – is modifiable. We already know that smoking makes many aspects of lupus worse, and this is just another reason for patients with lupus not to smoke. Interestingly, we also found that patients who had taken hydroxychloroquine, or Plaquenil, had a lower risk of experiencing a blood clot. Lupus patients are often on this medication because it also helps to treat arthritis and rashes, so the fact that it may help to prevent blood clots was an encouraging discovery.

Our research group is now trying to identify additional genes that make lupus patients at greater risk for thrombosis. As with many aspects of lupus, ethnicity also seems to influence a lupus patient’s risk of thrombosis, and we are currently studying these differences across several ethnic groups, including Caucasians, African-Americans, Asian-Americans, and Hispanics. If we can understand more about the risk factors for blood clots in lupus patients, we hope to be able to prevent such events from occurring.
Genes, Environment, and Lupus Outcomes
Ilana Richman

Systemic lupus erythematosus (SLE or lupus) is a chronic autoimmune disease that exhibits some striking and perplexing patterns among populations. Lupus is three to four times more common among African Americans than among Caucasians. Lupus is also more common among Latinos and Asian Americans than among Caucasians. Lupus is not only more prevalent in these populations, but it is often more severe. African Americans, Asians, and Latinos, for example, all have higher rates of renal involvement than Caucasians.

While these differences have been well documented, our understanding of why such disparities exist is still incomplete. Genetics likely plays a role, but environmental factors, such as access to adequate health care, financial security, patient-doctor communication, stress, and education may also contribute.

An ongoing study at UCSF is designed to investigate the factors that contribute to disparities in lupus outcomes. This study focuses on a diverse set of lupus patients and, using genetic information gathered as part of the Lupus Genetics Research Projects, will explore the contribution of genetics to disparities. The study will also consider how other factors, like patient education, financial security, ability to access medical care and health-related behaviors, may affect lupus outcomes. By looking at both genetic and non-genetic factors, we hope to gain a more complete understanding of why disparities in lupus exist.

Elucidating the relationship between genes, environment, ethnicity, and lupus will allow for targeted interventions that will one day help to alleviate the disparities we see today.
The Discovery of Lupus Susceptibility Genes

Lupus is caused both by strong genetic and environmental factors. New understanding of the genes that contribute to lupus is beginning to offer insights into disease progression and may help identify possible new targets for treatment. In the 1970’s, researchers knew of only one gene that increased risk for development of lupus. For several decades progress in identifying genes contributing to lupus was slow. The publication of the human genome sequence in 2001 offered researchers a wealth of new tools and technologies for identifying disease genes. In the past 5 years, research and understanding of lupus genetics has flourished.

This was a very exciting year for lupus genetics due to the publication of several high-profile genetic studies that identified many additional lupus susceptibility genes. These studies took advantage of newly developed technology for genome-wide studies. Researchers are now able to identify disease risk genes by using a large number of genetic markers scattered across the entire genome. These studies examine nearly half a million genetic markers at one time!

Three genome-wide association studies published by this research group and others in the New England Journal of Medicine and Nature Genetics identified over 6 new genes associated with lupus. One of the genes identified is the TNFAIP3 gene discussed on page 5 of this newsletter. Many of these genes influence the immune system’s function and regulation. Through your participation in the UCSF Lupus Genetics Project, you contributed to these important studies. Although researchers are beginning to identify lupus susceptibility genes, they still do not know enough to develop a genetic screening test for lupus. Further research on the genes identified in these recent studies will shed light on disease progression as well as uncover potential new targets for treatment.

Do Patients with Rheumatoid Arthritis and Their Doctors Agree?

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease that can cause significant disability, economic losses, and increased mortality. Clear communication between patient and physician is essential not only for proper diagnosis of this disease, but also to accurately assess patients’ symptoms and explain risks and benefits of treatment. With new and potentially transforming treatments for RA, awareness of patient-physician agreement on symptom assessment is critical to the safe and effective management of RA.

Dr. Jennifer Barton, Assistant Professor of Medicine at UCSF, recently received funding from the American College of Rheumatology to examine to what degree patients with RA and their rheumatologists disagree. Working under the mentorship of Dr. Lindsey Criswell and with the UCSF Rheumatoid Arthritis Cohort, Dr. Barton has found that some 30% of patients with RA do not agree with their physicians on a simple assessment of how active their arthritis is. In the majority of cases where patients and their rheumatologists differ by more than 25% on how active they think their arthritis is, physicians underestimate what the patients report. In this preliminary study, patients with more swollen joints were more likely to agree with the doctor. The other striking finding was that a patient with a positive screening test for depression was more likely to rate disease activity higher (worse) than the doctor. How could depression be related to doctors underestimating patient-report of disease activity? One theory is that patients with depression have poorer communication with their doctors. While depression has been shown to be associated with increased pain and worse function among RA patients, no study has explored the relationship of depression and patient-physician disagreement over disease activity.

These preliminary results highlight two main points. The first is that nearly one-third of the time, patients and physicians disagree about how active a patient’s arthritis is. The second is that depression or depressive symptoms in patients with RA may lead to physician underestimation of disease activity or suboptimal patient-physician communication in RA. Further research to explore factors that may contribute to such discrepancies between patients with RA and their doctors in measuring disease activity are needed. Dr. Barton is grateful to all of the patient participants in the UCSF RA Cohort who have made this research possible. The ultimate goal of her research is to improve communication between patients with RA and their health care providers.

Give a Little Bit

Blood samples are very important to our research since they provide a rich source of DNA.

If you are willing to donate blood and have not done so, please contact us toll free at 1 (888) 223-3067 extension 1

There are two simple ways to provide a blood sample from anywhere in the country. There is no charge to you and we will reimburse you $25 for your time and effort.

We can mail a blood kit directly to your home for you to take to your physician’s office or a local lab

OR

Visit us at UC San Francisco to have your blood drawn.
Highland Hospital Recruitment
Jessica Wolf and Ruby Harrison

Since recruitment for this study is nation-wide, it is not always possible for us to meet each lupus and RA patient in person. We feel very fortunate to have the opportunity to attend a local rheumatology clinic at Highland Hospital in Oakland, California, where we have the ability not only to meet our participants, but also to recruit an ethnically diverse group of patients. After almost two years of attending this clinic, over 100 lupus and over 100 RA patients have been successfully enrolled in the study!

“People don’t know what it’s like [having lupus],” says Cherity in a recent interview. Cherity is the 100th lupus patient enrolled in the study at Highland Hospital, where she says she joined the study to help other people and to raise awareness of lupus. We look forward to continuing our presence at Highland Hospital and meeting more patients like Cherity, who are enthusiastic about being part of the study.

We would like to express our deepest thanks to all the participants from Highland Hospital for contributing to our research, the nurses and staff for their continued kindness, and to all the doctors, in particular, Doctors Michael Neuwelt, Brain Kaye, and David Daikh, for their support and dedication to the project.

Dr. Neuwelt, Chief of Rheumatology Highland Hospital

Your Heritage and Your Lupus Symptoms

Lupus is one of the most complex autoimmune diseases. Lupus symptoms vary among those affected from skin rashes to organ inflammation to kidney disease. As Ilana Richman describes in her article on page 3, the incidence and severity of lupus varies between ethnic groups. Researchers hypothesize that the differences in disease rates among ethnic groups are due in part to differences in the genetic makeup of these groups.

In addition to genetic differences among individuals from different ethnic backgrounds, there are also genetic differences within major ethnic groups (for example northern Europeans and southern Europeans have a slightly different genetic makeup). Recently, Dr. Sharon Chung and colleagues conducted a study to determine if differences in northern and southern European ancestry are associated with certain lupus symptoms. Dr. Chung found that northern European ancestry is associated with an increased risk for photosensitivity and discoid rash. Interestingly, northern European heritage is also associated with a decreased risk for production of autoantibodies to double-stranded DNA and phospholipids (discussed on page 2). Both photosensitivity and discoid rashes develop by exposure to sunlight. This is of particular interest since people from northern Europe are exposed to sunlight less than southern Europeans and may have developed increased capacity for sunlight absorption. Dr. Chung and colleagues postulate that this additional sunlight absorption may lead to additional sun-induced damage resulting in discoid rash and photosensitive reactions.

This research highlights the role of genes in determining lupus disease manifestations and progression. We hope that continued research into the genes that determine which of the diverse lupus symptoms a patient will get can lead to better diagnostic and prognostic tools for doctors.
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 let us know if:

• You have moved
• You need a replacement DNA collection kit or forms
• You are willing to donate a blood sample
• Additional family members have developed an autoimmune disease

Thank you for your participation in this important research!

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

Save Trees and Help us Go Green!

To receive future newsletters like these by Email simply-

Visit our website http://medicine.ucsf.edu/lupus

Click on Newsletters and follow the instructions under GO GREEN!

Inside This Issue:

Blood clots and lupus...............................2
RA research in the Netherlands............2
Study participation chart.......................3
Genes, environment, and lupus.............3
Advancing treatment of RA....................4
Genome screens for lupus risk genes......4
Recruitment at Highland Hospital.........5
Your heritage and lupus symptoms.......5
Two new risk factors for lupus and RA...5
Keep in touch and Go Green!.............6