

# Personalized Medicine

## Research Project



## PMRP used for finding links between genes and proteins that contribute to immune diseases

Steven Schrodi, Ph.D.

Our immune system is made up of special cells that help fight against infections like the common cold, ear infections, or Lyme disease. Without a functioning immune system, people are affected by severe infections from bacteria, viruses and fungi. Important molecules called cytokines aid communication between immune cells. This enables coordination of actions needed to combat infections and to avoid the immune system attacking the body's own cells. Found in blood, cytokines are small proteins that tell cells where to go and what to do. There are different types of cytokines that perform many functions.

During an infection, large amounts of different cytokines are made. People with severe allergic reactions and diseases like rheumatoid arthritis and multiple

sclerosis can also have higher cytokines and imbalances among cytokines. Recent studies have shown that elevated cytokine levels over a long time could put people at risk for many diseases like heart disease, cancer, Alzheimer's and diabetes. How this happens is not well-understood. If we can figure out which cytokines are contributing to these diseases and how they are doing that, we might be able to help treat these diseases. Fortunately, the PMRP is a wonderful resource to do these studies. We guessed that some people have higher levels of one or more cytokines than other people. We also guessed that some people might have higher cytokines because of the versions of the genes that they have, just like how height and hair color are controlled by versions of genes. If we can identify those genes, then it might give

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## From the Director, Center for Human Genetics



**Murray  
Brilliant, Ph.D.**

PMRP has allowed us to make important discoveries in understanding how our genes contribute to our health. We have identified changes in specific genes that increase our odds for developing certain

diseases (such as age-related macular degeneration, type 2 diabetes and heart disease). The identification of these genes is leading to new ideas about treatments and drug therapies for these diseases. We have also identified changes in specific genes that predict how we will respond to common drugs. This has led us to develop new ways to help our doctors prescribe these drugs and prevent adverse drug

reactions. In a previous newsletter, we talked about a project to do just that: the eMERGE Pharmacogenetics (PGx) Project.

PGx is different from PMRP in an important way: PMRP is designed to discover genetic changes associated with disease and adverse drug reactions; participants remain anonymous and no individual results are returned. In contrast, PGx is designed to use information from PMRP and similar studies to develop clinical testing for people BEFORE they are prescribed certain drugs. This information is placed in their medical record and, at the time a prescription is written, their doctor is notified if there are potential problems with that drug for that person.

Currently, your doctor prescribes a drug for you and it works most of the time. Some people, however, will have a harmful reaction to that drug and so their doctor will then try another drug. PGx

aims at giving the right drug the first time. Changing medical practice is never easy, but we have already completed recruitment of 750 Marshfield Clinic patients and have nearly finished development of a system that will signal if patients' genes make it more likely that they will have adverse reactions to three common drugs: simvastatin (Zocor), colpidogrel (Plavix) and warfarin (Coumadin). The recommended drug dose to be given to a patient based on the patient's gene changes has been developed, and we have begun to put this in the medical records of the 750 participating patients.

We hope that demonstrating the benefits of this program will lead to an expansion of this type of testing to more people, and that such testing will become standard medical care in the future. You, the participants of PMRP have made this, and many other advances and improvements in healthcare, a reality.

## From the eMERGE Principal Investigator



**Cathy  
McCarty, Ph.D.**

### ***Greetings from Duluth!***

By the time you receive this newsletter, we will be into the final year of funding for the second 4-year grant from the National Human Genome Research

Institute (NHGRI) for the eMERGE project. The Funding Opportunity Announcement (FOA) to extend the eMERGE network another four years has just been released, with a deadline this fall. We have been a very successful site, so I hope that they will continue to fund us in the third cycle. The National Human Genetics Research Institute (NHGRI) struggled with balancing limited grant dollars towards new genomic discoveries using the existing DNA samples in bio-banks, versus translation of genetic discoveries into healthcare systems. There will be some of both.

In Duluth, we are just finishing a genomic medicine pilot study for age-related macular degeneration (AMD) through the eMERGE project. Approximately 100 people aged 50+ years with a family history of AMD were recruited to have a genetic test and receive a risk score for their likelihood of developing AMD over the next 10 years. The response to the testing was very positive, with everyone saying that they would be tested again, and many people making changes, such as wearing a hat and quitting smoking, to decrease their risk of AMD.

eMERGE has been fun because of the collaborations with many scientists across the US. When we first submitted our grant application in the fall of 2006, we proposed to conduct genetic testing of 1500 DNA samples from people who had age-related cataract and 1500 DNA samples from people who did not have age-related cataract. Each of the five eMERGE study sites proposed to look at different health outcomes (diabetes, dementia, heart rhythms, peripheral

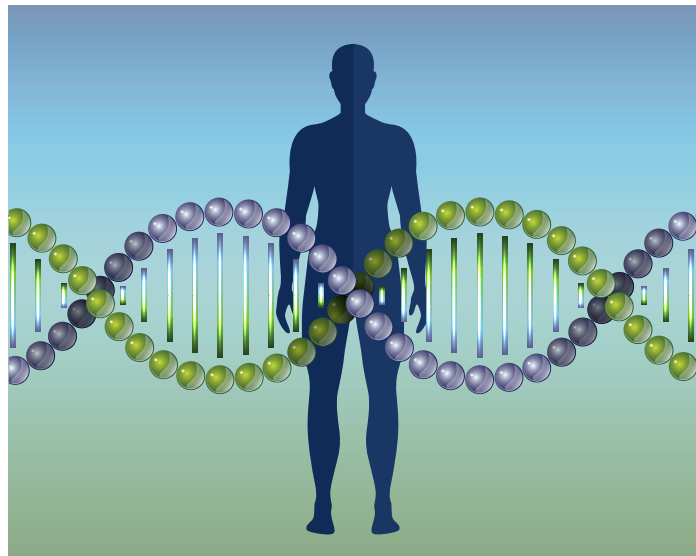
arterial disease), assuming that 3000 samples per site would be enough for statistical analyses. We all discovered that we needed to share de-identified data across sites to increase the sample size for genomic discoveries.

The eMERGE network has been a model for sites working together in the interest of science to improve healthcare. For the most part, this has happened without egos getting in the way, which is unfortunately not always the case in science! We have friendly competition within the network and we were very proud to be one of the first sites to complete enrollment for the pharmacogenetics study (eMERGE PGx).

As always, this could not happen without the support of PMRP participants and the Marshfield Clinic community. Thank you one and all! We have a lot to be proud of.

# Discovering disease genes using PheWAS

Scott Hebbring, Ph.D.



Our understanding of the human genome has advanced dramatically over the last few years as a result of significant technological breakthroughs. Unfortunately, identifying genes that can be used to predict, prevent, or treat common human diseases has been a challenge. This may be due in part to the methods that have been used to study such diseases.

In clinic populations, including PMRP, individual diseases are often studied at the genetic level. These studies begin with a disease of interest and attempt to look for genes that are linked to that disease; this method is called a “phenotype-to-genotype” approach. If the disease being studied is not caused by strong genetic factors, or the human genome is too complex to identify the strong genetic factors, then such studies focused on a specific disease can result in inconclusive results.

To address these challenges, investigators at the Marshfield Clinic are applying a novel strategy that creatively uses the invaluable assets of PMRP and Marshfield Clinic’s extensive electronic medical record (EMR) system to conduct what is called a “Phenome-Wide Association Study” (PheWAS).

Where most human genetic studies focus on a “phenotype-to-genotype”

approach, PheWAS reverses this approach in a “genotype-to-phenotype” manner. Instead of focusing on a specific disease, PheWAS focuses on a specific gene and attempts to link many diseases to that individual gene. At the Marshfield Clinic, researchers are attempting to link individual genes to nearly 5,000 diseases.

An advantage of the PheWAS method is

that thousands of diseases can be studied at the same time. As such, many understudied conditions can be studied at the genetic level. For example, a recent PheWAS was conducted in PMRP on a gene that is well known to be linked to multiple sclerosis (MS). In this study, not only was MS linked to the gene, as expected, but many other conditions, including rosacea, were also linked to the same gene.

MS is a debilitating disease that affects a patient’s brain and is very difficult to study because of the tissues that are affected. In contrast, rosacea is an extremely common condition that results in irritation of the skin on the face. Although some rosacea patients experience uncomfortable symptoms, and rosacea may be an easier disease to study because of ready access to samples of the affected skin tissue, rosacea is not considered a severe condition and is often under-studied.

If MS and rosacea share a common disease process, scientists can begin to study rosacea to learn more about MS. What is important about finding the link between MS and rosacea is that drugs used to treat rosacea may be used to treat MS, or vice versa, if both diseases share a common genetic cause.

## Medical terms

- **Immune system:** the body’s natural defense system that helps fight infections
- **Allergic reaction:** an over-reaction of the immune system
- **Pharmacogenetics:** the study of how genes are related to a person’s response to drugs/medicines
- **Adverse drug reactions:** unwanted and/or harmful reactions in our bodies caused by the drugs we take
- **Risk score:** a method for finding out the chances that a person will get a certain disease within a specific time period
- **Phenotype:** clinical information about a person. Examples are hair color, weight, and the presence or absence of disease
- **Phenome:** the set of all phenotypes for a person
- **Genotype:** information about the gene itself
- **Genome:** the complete set of genes present in an organism

A challenge of the PheWAS method is to identify the genes that should be studied for their roles in disease from a list of thousands of genes in the human genome. Many genes in the genome have no known relationship to human diseases. To address this challenge, Marshfield Clinic scientists are focusing on genes that harbor genetic variants that shut down genes. An advantage of this strategy for finding disease genes is that it helps scientists to explain how a gene linked to a disease affects the biological processes that cause the disease. PheWAS may provide an effective approach for studying how human genetics can be used to perform personalized medicine.



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us clues as to how we might help fix or prevent many of these diseases.

To study these cytokines, we measured nine important cytokines in samples from blood taken from over 2,000 PMRP members at enrollment. It turns out that some people have much higher levels of some cytokines than other people. For example, for one cytokine, interleukin-17A, we found that 40 people out of the 2,000 had more than 5-times the average level of interleukin-17A. No one had found this before. Interestingly, interleukin-17A was recently found to be involved in asthma, Crohn's disease and psoriasis, among other diseases. If we reduce interleukin-17A in these 40 people, can we help prevent these diseases? We don't know – more studies are needed.

So, why do some people have higher levels of these cytokines than others? My background is in mathematical models in genetics, so I was very interested in discovering if cytokine levels were controlled by genes. We have previously used amazing technology to measure about 500,000 DNA pieces in many PMRP samples. This technology measures DNA that we know varies among people – some people might have one version, whereas other people have different

versions. We tested each piece of DNA to see if it was linked with the cytokine levels. That is, we tested to see if some versions had, on average, higher cytokine levels compared to other versions. We used statistics and fast computers to do the calculations quickly. We were excited to find that versions of a gene called relaxin/insulin-like receptor 3 (RXFP3) change the levels of another cytokine, interleukin-6. Interleukin-6 helps fight many infections like the whooping cough bacteria. But, interleukin-6 has also been found to be higher in people with a build-up of plaque in their arteries, diabetes and Alzheimer's. This is a new discovery and it may turn out that a drug can be made to modify how RXFP3 works. Such a drug could possibly reduce the risk of these diseases.

My colleagues and I want to sincerely thank you for supporting and volunteering for the PMRP. We are working hard to discover patterns in genes and cytokines that might cause diseases. Once we better understand how these diseases work, doctors may be able to diagnose diseases earlier and other researchers may develop treatments to delay or prevent these diseases. Without involvement from PMRP participants, we would be unable to do this research at Marshfield.

## Contact Us

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## Thank You

This publication was supported by Grant No. 01HG006389, from the National Human Genome Research Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Institute.