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Marshfield Clinic
Research Foundation

Personalized Medicine
Research Project

PMRP used for studying angioedema caused by an adverse drug reaction

Researchers have used genetic data from the Personalized Medicine Research Project (PMRP) to study the causes of angioedema, the swelling of tissues in the body. The study focused on patients who took drugs known as angiotensin converting enzyme (ACE) inhibitors. Most of the genetic data used in the study was obtained because of the PMRP's participation in the eMERGE network (www.gwas.net). Cathy McCarty, Ph.D, is the Principal Investigator of the eMERGE grant and Murray Brilliant, Ph.D., is the co-Principal Investigator.

ACE inhibitors are drugs used to treat high blood pressure. In rare cases, these drugs can cause angioedema. Swelling due to angioedema can involve the face, lips, tongue, upper airway and even the bowel, and can be painful. Swelling of the tongue and upper airway can make it hard to breathe and can lead to death. These unwanted effects of ACE inhibitors are known as "adverse drug reactions". More than 40 million patients in the United States take ACE inhibitors but only about 1% to 6% of them develop angioedema. The chances of getting angioedema is higher for persons of African American ancestry, women, older patients, smokers, persons with seasonal allergies, and patients who use drugs that lower the body's ability to fight infections. Because only some persons who take ACE inhibitors get angioedema, researchers performed a study to find out if a person's genes make it more likely that he or she will get angioedema.

The study used two methods to find a link between genes and angioedema. One was to conduct a general survey of small changes that are present across all human genes, known as a genome-wide association

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Inside

From the Director, Center for Human Genetics

Murray Brilliant, Ph.D.

"Journeys"

We begin a journey thinking we know where we are going, but detours and other opportunities often lead us to a completely different place. I began my career studying why mice come in so many different colors. I was able to isolate and identify a few of the genes that contribute to mouse coat color. I also found that these same genes are associated with hair, eye and skin color in people. I then developed a method to predict what people will look like based on their DNA. Those predictions are quite accurate and are now used in some criminal cases. If we can predict what a person may look like from DNA, why can't we predict what diseases they are more likely to get and what medicines will work best for them. That is what brought me to Wisconsin and the Marshfield Clinic 5 years ago. PMRP allows us to discover ways to improve and personalize healthcare. I still work with those genes that I found in mice many years ago. When they work well in us, we have darker hair, eyes and skin. When they work less well, our features are lighter. When they don't work at all, we have albinism (albino).

The study of people with albinism has led me to the far corners of the earth. I have worked with populations in Arizona, Maryland, Puerto Rico, Panama, Indonesia, Scotland, Tanzania and Australia. Because people with albinism have vision problems, the understanding of the function of these genes is important and has led to two clinical trials to try to improve vision in these people. PMRP offers us the hope that as we understand the function of our 23,000 genes and the small differences that each of us have in these genes, we can improve health care for each and every one of us. As participants in PMRP, you have made real and significant contributions to improving health care. Thank you.

From the eMERGE Principal Investigator

Cathy McCarty, Ph.D.

In my column last summer, I mentioned that there would be a meeting organized in January 2014 to discuss the future of the eMERGE network and to please stay tuned for more information. Here is the information. eMERGE was originally funded by the National Human Genome Research Institute (NHGRI) for four years, with no anticipation of additional funding. Because of the many successes in phase 1, NHGRI made funds available for a second phase of four years and we were successful when we applied for that grant. We are now more than half way through eMERGE 2. Our Project Officer at NHGRI started talking about the possibility of a third round of funding for eMERGE and organized a one-day meeting with outside experts to review our progress and make recommendations about the direction for phase three, and it seems likely that funding for eMERGE 3 will be made available. Because of the snow storm in the Washington DC area, the on-site meeting was changed to a webinar (what an amazing winter this year!). Eight panels were held to discuss possible eMERGE 3 topics: 1) discovery versus implementation, 2) EMR and clinical phenotyping, 3) EMR and genomic discovery, 4) genomic testing, 5) consent, education, governance, 6) return of genomic results, 7) EMR integration, and 8) genomic medicine and pediatrics. A number of opportunities for future genomic discovery and implementation were identified that are uniquely suited to the advantage of multiple clinical sites that work well together. We anticipate the release of a grant announcement later this year.

In my previous columns I have taken the opportunity to thank our wonderful staff when they have departed and wished them well on their next adventures. This time I have the pleasure of welcoming someone back to our research team and Marshfield Clinic Research Foundation. Peggy Peissig has been with the eMERGE research team since our initial grant submission and has been with PMRP since the early planning phases of the project. She took a position with Security Health Plan for two years and recently returned to the Research Foundation after she completed her PhD to take a scientist position with the Center for Human Genetics. Congratulations Dr. Peissig and welcome back to the Research Foundation and a bigger role with eMERGE – we missed you!

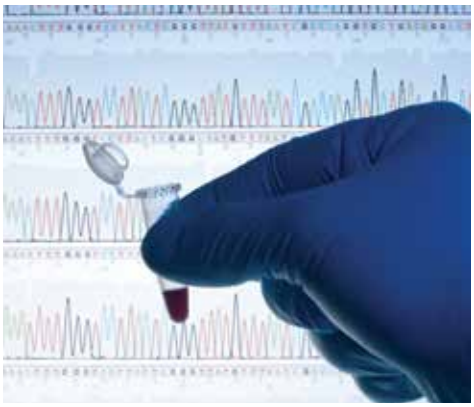
We recognize the contributions of Phil Boehning (1940 – 2014) to the PMRP Community Advisory Group (CAG). He answered our call for new CAG members in 2007. He was particularly interested in PMRP because of a medical condition that ran in his family and contributed to our discussions about sharing genetic results with patients. Our thoughts go out to his family.

I can't end without a few words about my son. He turns 15 in February (and can get his driver's permit!) and has grown up hearing about PMRP and the wonderful genetics research at Marshfield Clinic Research Foundation. His primary care physician is already personalizing his health care on the basis of family health history. For him, that means early and regular cholesterol and blood pressure screenings, and he is not likely to escape kidney stones in his future. Do you know your family health history?!

New data enhances PMRP

Murray Brilliant, Ph.D.

The vision of PMRP is to aid research that can be used to improve health care through a better understanding of the genetic (and other) factors that contribute to our health and wellness. We believe that your genes have important information that can help us deliver the best health care for you. The results of studies using PMRP have already been used in the clinic to help reduce adverse drug reactions (see last issues' column on the Pharmacogentics Implementation Project, PGx). In addition, we now can predict risk for a few diseases where we have preventative treatments (such as Age-related Macular Degeneration).



Although we have learned much from our many studies, a lot more remains to be discovered. The human genome is very complex with 3 billion bits of information in each person's DNA. The ultimate goal of PMRP is to unlock the secrets of how these 3 billion bits of information are associated with disease. Currently, we have about 600,000 bits of information on about 5,000 people in PMRP. This is about to change dramatically. Through generous support from the Marshfield Clinic Research Foundation (MCRF) and the National Eye Institute (totaling almost $1 million), we will shortly add important new genetic data on 10,000 PMRP participants. This will improve our ability to discover new connections between genetic changes and health. Moreover, MCRF has received a new grant from Complete Genomics, Inc. Complete Genomics will provide us with the whole genome sequence (all 3 billion bits of information) for 300 people (worth nearly $3 million). Although we know that certain genetic variants are associated with specific disorders, testing a person's whole genome is not routine, is expensive, is not usually covered by insurance and remains controversial. Moreover, we are not allowed to return research results to individuals who are in PMRP. To estimate the lifetime benefit of the knowledge of these 3 billion bits of genetic data, we will determine the DNA sequence of 300 individuals who are deceased. Thus, we will determine the potential health benefits, savings in medical procedures and costs for each subject as if we had the genetic data over the lifetime of these people. This new project aims to understand if this type of testing could be beneficial, given the limits of today's knowledge. We expect to look at changes in DNA that are associated with adverse drug reactions, cancer risk, eye disease, heart disease, etc. There have been a few spectacular success cases where whole genome sequencing has resulted in life-saving treatment plans and a successful end of a complex medical odyssey. However, large-scale studies have yet to be performed to show that whole genome sequencing is an effective way to improve medical care and/or save costs on a population basis. This new study will allow us to determine the potential benefits of whole genome sequencing for the general population.

PMRP participants to be included in survey of 16,000 US adults

Cathy McCarty, Ph.D.

We received an "administrative supplement" to the eMERGE grant recently. The National Human Genome Research Institute (NHGRI) awarded us additional funds for the final two years of the eMERGE grant. We had a very short period of time last summer to write the grant. NHGRI chose to award the extra dollars to eMERGE because they had a specific research question that they wanted answered and were confident that the eMERGE network would be successful.

In 2011, the US Department of Health and Human Services issued a proposal to change the federal rules that guide human subjects research. One of the proposed changes would require participants to consent to use of their de-identified clinical information for research. These proposed changes have great implications for people like you who have participated in biobanks.

Little is known about the public's views on "broad consent" for research. NHGRI wants to find out what the public thinks. This project will answer two questions for NHGRI. First, what do participants think of the proposed requirement of consent for sharing of samples and data for research? Second, what research practices will have the greatest impact on willingness to participate after giving "broad consent"?

Along with the other eMERGE sites (see map, www.gwas.net), we will develop a survey to be mailed to a random sample of biobank participants and patients of the various healthcare systems. The surveys will be scanned into the computer at a central site and the information will be combined from across all eMERGE sites. The biobanks and populations served by the healthcare systems in the eMERGE network are very diverse. Therefore, the results of this very large study will represent a good cross-section of US adults.

Studies using the PMRP database

Genetic Terms

Genotyping: The process of finding out the genetic make-up of a person. Genotype is the information about the gene itself.

Phenotyping: The process of finding out clinical information about a person. Examples of phenotypes are hair color, weight, or the presence or absence of disease.

SNP: An abbreviation for "single nucleotide polymorphism", a small change in the base units that make up DNA.

GWAS: Genome-Wide Association Study. These studies look across a person's entire DNA as opposed to looking at one section of DNA, such as a gene.

Chronic Diseases

Chronic diseases are diseases that last a long time and that generally develop very slowly. Examples of these diseases are heart disease, stroke, cancer, and diabetes. These diseases cause most of the deaths around the world. Researchers are using the PMRP database to find out the causes of chronic diseases.

Genome-Wide Association Study of Coronary Artery Disease in the Personalized Medicine Research Project

Project leader: Ulrich Broeckel, M.D., Medical College of Wisconsin

Collaborators: Steven Schrodi, Ph.D. and Humberto Vidaillet, M.D., Marshfield Clinic; Deanna Cross, Ph.D., University of North Texas

Funding: National Heart, Lung and Blood Institute

The objective is to perform a genome-wide association study to identify susceptibility genes for coronary artery disease, myocardial infarction and its related risk factors. This study will improve our understanding of the interplay of genetic and traditional risk factors in coronary artery disease.

WGI Exome Sequencing to Identify Coding Variants for Myocardial Infarction

Project leader: Ulrich Broeckel, M.D., Medical College of Wisconsin

Collaborators: Murray Brilliant, Ph.D., Marshfield Clinic; David Page, Ph.D., UW-Madison

Funding: Wisconsin Genomics Initiative

A myocardial infarction is another name for a heart attack. The exome is the portion of our DNA that codes for genes. The aim is to sequence 40 PMRP participants that have been diagnosed with myocardial infarction but did not have the normal risk factors for heart attack, to identify the genetic variants that are most likely to be associated with this disease.

Molecular Markers for Non-Small Cell Lung Cancer Susceptibility

Project leader: Jill Kolesar, Pharm.D., UW-Madison

Collaborator: James Burmester, Ph.D., Marshfield Clinic

Funding: UW Carbone Cancer Center

The aim is to find genetic markers that predict the risk of getting lung cancer. Genetic material (DNA) from non-small cell lung cancer subjects will be compared to DNA from subjects who do not have cancer. Differences in the DNA patterns between the two groups may be a marker of lung cancer risk.

Integrating Genomic Data into a Computational Model for Improved Breast Cancer Diagnosis

Project leader: Catherine McCarty, Ph.D.

Collaborators: Peggy Peissig and Adedayo Onitilo, M.D., Marshfield Clinic; Elizabeth Burnside, M.D. and David Page, Ph.D., UW-Madison; Ulrich Broeckel, M.D., Medical College of Wisconsin

Funding: Wisconsin Genomics Initiative

This Wisconsin Genome Initiative pilot proposal aims to incorporate genetic polymorphisms with the risk factors that radiologists observe including the shape and margins of masses, the shape and distribution of micro-calcifications, and background breast density (all promising biomarkers for stratifying risk), as well as known demographic risk factors to improve risk prediction for breast cancer.

A Pilot Study of Age-Related Macular Degeneration in PMRP

Project leader: Murray Brilliant, Ph.D.

Collaborator: Catherine McCarty, Ph.D., Essentia Institute of Rural Health

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

The goal is to develop a predictive formula for age-related maculation degeneration using data from previous association studies and biological samples from the PMRP database.

Phase II – Predicting and Preventing Age-Related Macular Degeneration

Project leader: Murray Brilliant, Ph.D.

Collaborators: David Page, Ph.D., UW-Madison; Joseph Carroll, Ph.D., Medical College of Wisconsin

Funding: Wisconsin Genomics Initiative

The purpose of this study is to determine a predictive formula for those at high relative risk for age-related macular degeneration (AMD) based on previously identified genetic markers, age, sex, environmental factors and advanced retinal imaging. Prediction of AMD with high accuracy will allow for future therapies to be targeted to specific people and hopefully allow us to prevent AMD before it occurs.

Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project (eMERGE I) and Incorporating Research into Sight (eMERGE II)

Project leaders: Catherine McCarty, Ph.D.; Murray Brilliant, Ph.D.

Collaborators: Russell Wilke, M.D., Ph.D., Vanderbilt University; Norman Frost, M.D., UW-Madison; Marylyn Ritchie, Ph.D., Penn State University

Funding: National Human Genome Research Institute

eMERGE I: The aim of this study is to develop and validate electronic phenotyping formulas to identify cases of cataract and of reduced high density lipoprotein cholesterol (HDL-cholesterol or good cholesterol) in the PMRP, and also to quantify the impact of two environmental factors (cigarette smoking and statin use) on those diseases. Cataract and reduced HDL-cholesterol are two yet interrelated diseases. Update: This study has developed an approach to identify cataract cases using electronic health records. In addition, it has also shown that certain changes in the CNR1 gene appear to have a protective effect on the decrease in HDL cholesterol concentrations that typically accompanies weight gain. It has also shown that the LPL and ABCA1 genes are both involved in regulating HDL-cholesterol concentrations.

eMERGE II: This study will develop ways to use electronic medical records to identify cases of certain eye diseases. These diseases include ocular hypertension (the pressure inside the eye is higher than normal), glaucoma (damage to the nerve that carries information from the eye to the brain), age-related macular degeneration (disease that causes loss of central vision leaving only side vision intact), and tear film insufficiency (the eye does not produce enough tears to keep it moist). (Genet Med 2013 Oct;15(10:761-771.)

Metanomics Health and Marshfield Type 2 Diabetes Prediction

Project leader: Steven Schrodi, Ph.D.

Collaborators: Dietrich Rein, Ph.D. and Inken Padberg, Ph.D., Metanomics GmbH

Funding: Metanomics GmbH

About 90 percent of diabetes cases in the U.S. are Type 2, sometimes called "adult-onset" diabetes. This study will be used to replicate an existing metabolite-based predictive model for Type 2 diabetes. The study will also incorporate data from an exome-based GWAS and from metabolic/inflammatory biomarkers to improve Type 2 diabetes prediction.

Protein Tyrosine Phosphatase, Non Receptor Type 22 (PTPN22) Phenomics

Project leader: Steven Schrodi, Ph.D.

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Among persons with European ancestry, the PTPN22 gene has a SNP (known as R620W) that is related to the chances of getting a number of diseases. Many of these diseases involve inflammatory processes (a group of processes that the body uses to protect itself when there is an infection). Some of these diseases are type 1 diabetes, rheumatoid arthritis, and bacterial infections. The aim of this study is to find new diseases that are related to R620W. By discovering new relationships between R620W and disease, researchers can find out more about the role that the PTPN22 gene plays in human health.

Validation of biomarkers to distinguish aggressive from indolent prostate cancer

Project leader: George Wilding, M.D., UW-Madison

Collaborators: Tonia Carter, Ph.D., Christopher Cold, M.D., Marshfield Clinic

Funding: National Cancer Institute

Prostate cancer is a common type of cancer in older men. Most newly diagnosed prostate cancers are slow-growing and require no treatment (indolent cancer). However, some may progress and lead to death (aggressive cancer). It is a challenge for many doctors to identify aggressive prostate cancer, and researchers are trying to find chemicals in the body (biomarkers) that can help doctors to do this accurately. The aim of this study is to find out if a protein involved in cell survival can perform as a useful biomarker to identify patients with prostate cancer that is likely to become aggressive.

Pharmacogenetics/ Genomics

Pharmacogenetics is the study of how genes are related to a person's response to drugs/medicines.

A Pilot Study for the Identification of Severe Cutaneous Reactions and Genomic Risk Factors in Users of Anti-Epileptic Drugs

Project leader: James Burmester, Ph.D.

Collaborators: Robert Davis, M.D, Center for Health Research Southeast; Nandini Selvam, Ph.D., HealthCore; Maryam Asgari, M.D., Kaiser Permanente; Melody Eide, M.D., Henry Ford Health Services; David Margolis, M.D., University of Pennsylvania

Funding: US Food and Drug Administration

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are two forms of a life-threatening skin condition in which cell death causes the top layer of the skin (epidermis) to separate from layers underneath (dermis). The aim is to identify patients at Marshfield Clinic with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis and to estimate the number of cases that are potentially available for possible future research studies. The project will also genotype 100 random DNA samples from the PMRP population and determine the frequency of the HLA-A*3101 and HLA-B*1502 alleles.

Genotype and Clopidogrel/Proton Pump Inhibitor Interactions

Project leader: Amanda Hein, M.D.

Collaborators: James Burmester, Ph.D. and Michael Caldwell, M.D, Ph.D., Marshfield Clinic

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Clopidogrel is a medication used to prevent strokes and heart attacks in patients at risk for these problems. Proton pump inhibitors are a group of medications used to reduce the amount of acid produced by the stomach. By

using a clearly defined and stable epidemiologic research population, the goal is to analyze phenotypic and genotypic data of a subset of PMRP participants for possible Clopidogrel/ proton pump inhibitor interactions that may ultimately change the course of medical management for the cardiac and vascular patient populations.

Human Genetic Variation and Response to Metformin Therapy

Project leader: Melissa Simpson, D.V.M., Ph.D.

Collaborators: Catherine McCarty, Ph.D., Essentia Institute of Rural Health; SookWah Yee, Ph.D. and Kathleen Giacomini, Ph.D., University of California – San Francisco; Robert Davis, M.D, Center for Health Research Southeast; Russell Wilke, M.D., Ph.D., Vanderbilt University

Funding: Agency of Healthcare Research and Quality; Pharmacogenomics Research Network of the National Institute of General Medical Sciences; RIKEN Institute

Metformin is a drug used to treat diabetes. The goal is to assess whether single nucleotide polymorphisms in the OCT1 and/or OCT2 genes are more frequent among metformin-exposed subjects with type 2 diabetes who did not respond to metformin compared with metformin-exposed subjects with type 2 diabetes who were responsive to metformin.

PGPop: PharmacoGenomic Discovery and Replication in Very Large Patient Populations

Project leader: Murray Brilliant, Ph.D.

Collaborators: Peggy Peissig, Marshfield Clinic; Dan Roden, M.D., Michael Stein, M.D., Dana Crawford, Ph.D., Hua Xu, Ph.D., and Joshua Denny, M.D., Vanderbilt University; Marylyn Ritchie, Ph.D., Penn State University

Funding: Pharmacogenomics Research Network of the National Institute of General Medical Sciences

The aim is to establish a research network to study patient data on how drug (medicine) exposures are related to disease outcomes. The first studies will examine how certain drugs affect patients with asthma.

Validation of Vanderbilt's vancomycin pharmacokinetics GWAS

Project leader: Scott Hebbring, Ph.D.

Collaborators: Joshua Denny, M.D., Sara Van Driest, M.D., Ph.D., Vanderbilt University

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Vancomycin is commonly prescribed to treat penicillin-resistant bacterial infections, most notably Staph (Staphylococcus aureus) infections. The effectiveness of vancomycin is partly dependent on how quickly the drug is metabolized by the body. Investigators at Vanderbilt University identified multiple genetic markers that may predict the rate of drug metabolism. Investigators at the Marshfield Clinic are collaborating with Vanderbilt University to independently validate these findings.

MS and Rosacea: Genetics to Pathophysiology to Drug Repurposing

Project leader: Scott Hebbring, Ph.D.

Collaborators: Loren Rolak, M.D., Clayton Green, M.D., Christopher Cold, M.D., Marshfield Clinic

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Multiple sclerosis (MS) and rosacea are two common diseases that are highly prevalent in the Upper Midwest region of the USA. Recent studies suggest that these two diseases may share a common mechanism predicted by genetics. This study is designed to further clarify this shared genetic relationship and to determine if drugs commonly used to treat rosacea can be repurposed to treat MS.

Mixed Dyslipidemia Genetics

Project leader: Ariel Brautbar, M.D.

Collaborators: Steven Schrodi, Ph.D., Min He, Ph.D., Marshfield Clinic; Sarah O'Brien, M.P.H., University of Iowa

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Lipid-lowering medications (such as statins) work well for some people and do not work well for others. Proper cholesterol and triglyceride levels are thought to be important to good health. This study investigates genes that may help explain why these medications work well in some people, but not others.

Other Genetic Epidemiology Studies

Genetic Epidemiology is the study of the interaction between genes and environmental factors in causing disease in human populations and their patterns of inheritance in families.

Multiple Sclerosis Mapping through Sequencing of Shared Regions

Project leader: Steven Schrodi, Ph.D.

Collaborator: Loren Rolak, M.D., Marshfield Clinic

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Multiple sclerosis is a nervous system disease that affects your brain and spinal cord. Using well-characterized multiple sclerosis patients, this project is designed to first identify genomic regions that are shared among affected multiple sclerosis individuals but not unaffected controls through existing genotype data, and then to sequence the single most statistically-compelling shared region in an effort to discover specific sequence variants linked and associated with relapsing-remitting multiple sclerosis.

Prevalence of the Fragile X Premutation

Project leader: Murray Brilliant, Ph.D.

Collaborators: Elizabeth McPherson, M.D., Marshfield Clinic; Marsha Mailick, Ph.D. and Matthew Maenner, Ph.D., Waisman Center, UW-Madison; Mei Baker, M.D., Wisconsin State Laboratory of Hygiene and UW-Madison.

Funding: US Centers for Disease Control and Prevention

Fragile X is a genetic condition involving changes (mutations) in the FMR1 gene on the X chromosome. It is the most common form of inherited mental retardation. Some people may only have a small change in their FMR1 gene (called a pre-mutation) and may not show any signs of Fragile X. Other people may have bigger changes in the gene, called

a full mutation, that cause the symptoms of Fragile X syndrome. The goal is to identify Fragile X full mutations and pre-mutations in the PMRP population. (Am J Med Genet B Neuropsychiatr Genet 2013 Jul;162B(5):466-473.)

Th17 Activity Genome-Wide Association Study

Project leader: Steven Schrodi, Ph.D.

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic; Clinical and Translational Science Award through UW – Institute for Clinical and Translational Research

T helper 17 cells (Th17) are a group of cells in the immune system. They are thought to play a key role in autoimmune diseases (when the body attacks itself), such as multiple sclerosis and rheumatoid arthritis. The objective is to discover genetic regions that segregate alleles associated with the activity of the IL-23/IL-17 pathway as mediated through Th17 cells.

Nonsense SNP Phenomics

Project leader: Scott Hebbring, Ph.D.

Collaborators: Murray Brilliant, Ph.D., Marshfield Clinic; David Page, Ph.D., UW-Madison

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

A nonsense SNP is a small change in DNA that causes only a portion of a protein to be made. Because only part of the protein is made, the protein is not able to perform its functions within our bodies. This study is designed to identify common diseases, defined by medical diagnosis codes, which are associated with nonsense SNPs in genes that have been linked to specific human diseases.

Genome-wide association study of Staphylococcus aureus infection

Project leader: Sanjay Shukla, Ph.D.

Collaborators: Steven Schrodi, Ph.D., Zhan Ye, Ph.D., Marshfield Clinic

Funding: Philanthropic gifts in support of medical research at Marshfield Clinic

Methicillin-resistant Staphylococcus aureus (also called a super bug) is a significant public health problem in hospitals around the world. It can cause a variety of diseases in humans, including infections of the skin, bone and heart. If the infection is very severe, it can even lead to death. This study looked for genes that increase a person's chances of getting Staphylococcus aureus infection.

Pilot study of genetic polymorphisms associated with influenza-related hospitalization

Project leader: Edward Belongia, M.D.

Collaborators: Steven Schrodi, Ph.D., David McClure, Ph.D., Jennifer Meece, Ph.D., Tonia Carter, Ph.D., Marshfield Clinic; Jill Ferdinands, Ph.D., Centers for Disease Control and Prevention

Funding: Centers for Disease Control and Prevention

Influenza causes only a mild illness in most people, with no need for medical care. However, some people get a severe influenza infection that leads to a hospital stay or even death. This study aims to find out if certain genes make it more likely that a person will get severe complications from influenza.

Genomic Postmortem Research Project

Project leader: Murray Brilliant, Ph.D.

Collaborators: Simon Lin, M.D., Min He, Ph.D., Marshfield Clinic

Funding: Complete Genomics

The promise of Genomic Medicine is that genotyping for specific variants related to a person's risk of disease can be performed before development of a disease, and the genotype data can be routinely stored in electronic medical record (EMRs), allowing genotype-based advice to be delivered to doctors at the point of care. Doctors will use the advice to guide their decisions when providing care to individual patients. This study proposes to sequence the entire genome in 300 patients with long-term EMRs at Marshfield Clinic to determine (after the fact) if genomic knowledge could have positively influenced their medical care. This will help us to understand how whole genome sequencing could affect health care decisions in a population.

An integrated molecular approach to understand variation in iron metabolism

Project leader: Chris Vulpe, Ph.D., University of California – Berkeley

Collaborator: Murray Brilliant, Ph.D., Marshfield Clinic

Funding: National Institute of General Medical Sciences

Iron deficiency is a common human disease that may be partly caused by genetics. Iron overload is also a health concern for humans. The goal is to identify genetic variants that are associated with iron level in human blood. This will help us understand how genes cause iron levels to vary in our bodies.

Age-related macular degeneration (AMD) exome

Project leader: Murray Brilliant, Ph.D.

Funding: National Eye Institute

Age-related macular degeneration (AMD) is a major cause of blindness in the United States. The goals are to examine genetic variation in persons with and without AMD, and to identify rare and common genetic variants that occur more frequently in AMD patients. This will help to discover how AMD develops and what makes some persons more likely to get AMD.

For further information on these studies, please visit the PMRP website: www.marshfieldclinic.org/pmrp

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PMRP used for studying angioedema caused by an adverse drug reaction

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study (GWAS). The other was to examine a select group of genes that researchers think might play a role in angioedema based on what is known at present about the way angioedema develops. This is known as the "candidate gene" method.

The GWAS method suggested that two genes could be involved: the protein kinase C theta (PRKCQ) gene and the ets variant 6 (ETV6) gene. They both regulate how the body fights infections. These genes could provide a clue as to why persons with seasonal allergies and those who use drugs that make it harder for our bodies to fight infections are more likely to get angioedema.

Using the candidate gene method, researchers found that the neprilysin (MME) gene could affect a person's chances of getting angioedema. Neprilysin is a protein that helps to break down another protein, known as bradykinin, in our bodies. Bradykinin works by causing blood vessels (e.g. veins and arteries) to get wider, and it can also cause fluid to leak out of the blood vessels into the surrounding tissues. The fluid in the tissues causes the tissues to get larger, leading to the swelling of the tissues that we call angioedema.

Researchers also noticed that no gene in this study had a very strong link to angioedema. This could be because there were only a small number of patients in the study. However, other studies with even smaller numbers of patients have been able to identify genes that cause adverse drug reactions. Another reason might be that no single gene has a large effect on a person's chances of getting angioedema. It is possible that angioedema in patients who use ACE inhibitors arises because of the small effects of many genes working together. There could also be contributions from other factors that are not related to genes, such as age and whether a person smokes cigarettes.

This study is another example of the great value of the PMRP for finding out the causes of the unwanted side effects of drugs. While it did not find any strong links between specific genes and angioedema, it identified three genes that can be examined further for a role in causing angioedema in patients who use ACE inhibitors. We are grateful to PMRP participants for making this research possible!

"Genetic variants associated with angiotensin-converting enzyme inhibitor-associated angioedema," Guillaume Pare, et al. Pharmacogenetics and Genomics 2013;23:470-478.

Contact Us

This newsletter is a publication of the Personalized Medicine Research Project, Marshfield Clinic Research Foundation, 1000 N. Oak Ave., Marshfield, WI 54449-5790.

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PMRP Advisors

Thank You

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