Marshfield Clinic®
Research Foundation

Personalized Medicine
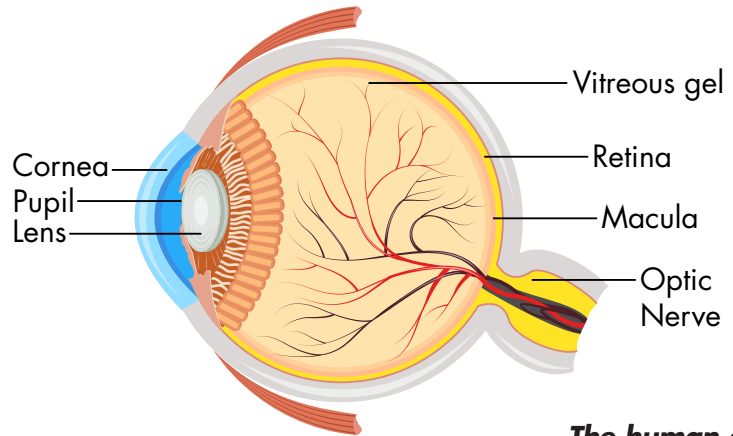## Research Project

Cornea
Pupil
Lens

Vitreous gel
Retina
Macula
Optic Nerve

The human eye

Age-related macular degeneration

Welcome to our first issue dedicated to a single disease! In this issue, we focus on age-related macular degeneration (AMD). We hope to make you aware of the exciting research that scientists are doing on AMD, using PMRP.

AMD is a common eye disease in the elderly. The macula is a small area of the retina – a layer of tissue lining the back of the eye and containing light-sensing cells. The macular is the part of the retina that allows us to have central vision – the ability to see objects that are straight ahead of us. The macular also is responsible for our ability to see details clearly, e.g., when reading street signs or threading a needle. AMD develops when the macula degenerates as part of the natural aging process.

A blurred area near the center of vision is a common symptom as AMD progresses. Over time, the blurred area can increase in size and there might be dark areas in the central vision. This can advance to blindness in the central vision. AMD does not normally affect side vision.

There are two types of AMD: dry and wet. Most AMD patients are diagnosed with the dry form. Patients with dry AMD have yellow deposits, called drusen, beneath the retina. As AMD advances, the drusen increase in size and number. Therefore, doctors check for drusen to make a diagnosis of AMD. About 10 percent of AMD patients are diagnosed with the wet form. In wet AMD, abnormal blood vessels leak blood and fluid into the retina causing vision to be distorted. The wet form can cause more damage to central vision than the dry form.

In the early stages of AMD, most people do not have symptoms or loss of vision. Doctors use eye examinations to detect AMD. Therefore, it is important to have a regular eye examination. The American College of Ophthalmology recommends that people between the ages of 55 and 64 years have a comprehensive eye examination every one to three years. People age 65 years and over should have a comprehensive eye examination every one to two years.

From the Director, Center for Human Genetics

Murray Brilliant, Ph.D.

Research scientists from around the world who attended the meeting on AMD in Bavaria, Germany.

"Journeys"

We begin a journey thinking we know where we are going, but sometimes we end up in the place where it all started. In mid-September I travelled to Bavaria to meet with fellow research scientists from all over the world. We are working together as part of the world's largest effort, to date, designed to uncover the genetic basis for Age-related Macular Degeneration (AMD). PMRP contributed one of the largest shares of the data used in this study – with nearly half of PMRP members (about 10,000) included in the study. With funding from the Marshfield Clinic and the National Eye Institute of the National Institutes of Health, we were able to detect the genetic differences between people with AMD and those who do not have AMD. The results of this study will be published soon and demonstrate that AMD is now one of the most predictable conditions among diseases associated with several different genes. Identifying the genes involved and understanding what they do may lead to new treatments for AMD.

PMRP is an amazing resource for biomedical research. Most of the members of PMRP had ancestors who moved to central Wisconsin between 1870 and 1890. These early settlers came in search of a better life. Most of them came here from Bavaria (Germany). It seems fitting that the volunteers in PMRP honored these ancestors by contributing to critical research organized in Bavaria that we hope will one day help prevent blindness in millions of people.

Outside the great Regensburg Cathedral, Bavaria, Germany.
Left to Right: Iris Heid, Murray Brilliant, Sylvia Pfreintner

From the eMERGE Principal Investigator

Cathy McCarty, Ph.D.

I blame it on eMERGE. I am back in school, a graduate program by distance in bioethics. My growing interest in bioethics has been sparked by eMERGE. As you have heard through the last seven years of the National Institutes of Health-funded eMERGE grant, community engagement and ethical issues are at the forefront of our discussions related to genomics research and return of results to research participants. Engagement on these issues is one of the three overall eMERGE study aims. We are considered leaders in community engagement around genomics research. An example of this is the PMRP Community Advisory Group (members listed on the back page of the newsletter) that has been used as a model by other eMERGE sites. We have had visits to our Community Advisory Group meetings by the eMERGE Program Officer from the National Human Genome Research Institute (NHGRI) and colleagues from other eMERGE sites, including Mayo Clinic and Northwestern University.

Studying is a good diversion from waiting to hear about our application for an eMERGE 3 grant. The grant proposal was submitted in November 2014 with Murray Brilliant and Peggy Peissig from Marshfield Clinic, Marylyn Ritchie from Penn State University, and me as Co-Principal Investigators. Every great study needs a great acronym. eMERGE stands for electronic medical records and genomics. The acronym for our current eMERGE grant locally is IRIS which stands for "incorporating research into sight". The acronym for the local eMERGE 3 grant that we submitted was GENIE which stands for "genomic implementation and engagement". (Yes, we do spend far too much time and have far too much fun coming up with acronyms!).

Let me briefly describe the process of applying for the eMERGE 3 grant. As mentioned in previous newsletters, there was a meeting organized by the NHGRI, and held last January in Washington, D.C. during a snow storm, to discuss eMERGE 2 and to consider opportunities for eMERGE 3. Staff at the NHGRI took information from that meeting and got approval from the governing council of NHGRI to issue a "Request for Funding Announcement" that was released on July 9, 2014 (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-14-025.html). The grant application was due on November 12, 2014 and was submitted a day early after many, many hours of writing from various members of the research team. A "special emphasis panel" will meet in person over a full day to review all of the grant applications in the spring of 2015. The grants will be scored and ranked according to their scores, with the lowest scores being the best. If we are awarded the grant, it will start in summer of 2015. Wish us luck!

PMRP used to study eye damage in age-related macular degeneration

Researchers have used PMRP to study very early changes in the eye that might lead to age-related macular degeneration (AMD). AMD can go unnoticed until later stages when vision loss begins to occur. However, it is important to detect the disease at an earlier stage when treatment can delay or lessen the amount of vision loss. "Knowing more about the early stages of AMD can help doctors provide timely, preventative treatment to patients to reduce the chances of developing vision loss," stated Murray Brilliant, Ph.D., a senior researcher on the study and the lead investigator of the PMRP.

About 1.75 million persons in the US have late-stage AMD with vision loss. By the year 2020, it is expected that about 3 million people in the US will have vision loss due to AMD. Persons more likely to have AMD are those who are over age 60, are female, have a lighter eye color, are overweight, have high blood pressure, are smokers, or have a family member with AMD. While the disease is associated with aging, research shows that variations in our genes contribute to our risk of getting AMD.

To detect early signs of damage to the eye that might cause AMD, researchers gave eye examinations to 40 patients who had never been diagnosed with AMD. Four types of tests were done. These tests are the standard eye tests that a patient gets during a regular eye examination. First, doctors took photographs of the inside of the eye to look for yellow deposits beneath the cells that sense light. Deposits that are medium-to-large in size could mean that AMD has developed. Second, doctors used light waves to capture images of living eye tissue so that they could view the structure of the inside of the eye. This allowed doctors to check if layers of tissue in the eye showed damage. Third, doctors checked the ability of the cells of the eye to sense light. Fourth, doctors checked how closely packed together were the light-sensing cells of the eye. Cells that are spaced too far apart can affect how sharp an image appears when a person sees.

The results of the four eye tests showed that early damage to the light-sensing cells inside the eye was present in some of the patients. However, this damage was not

Amsler Grid

The Amsler Grid is a tool that eye doctors use to test for age-related macular degeneration. You can also use the grid at home to check your vision. However, using the grid does not mean that you should avoid regular visits to your eye doctor.

How to use the Amsler Grid

- Do not remove glasses or contact lenses normally used for reading

- Hold grid at eye level about one foot away in a well lit room

- Cover one eye fully and focus on the center dot with the uncovered eye

- Repeat with the other eye

If the grid lines look wavy or broken (for example, as in the grid below), or if there are blurred or missing patches on the grid, this could be a symptom of age-related macular degeneration. You should report this to your eye doctor.
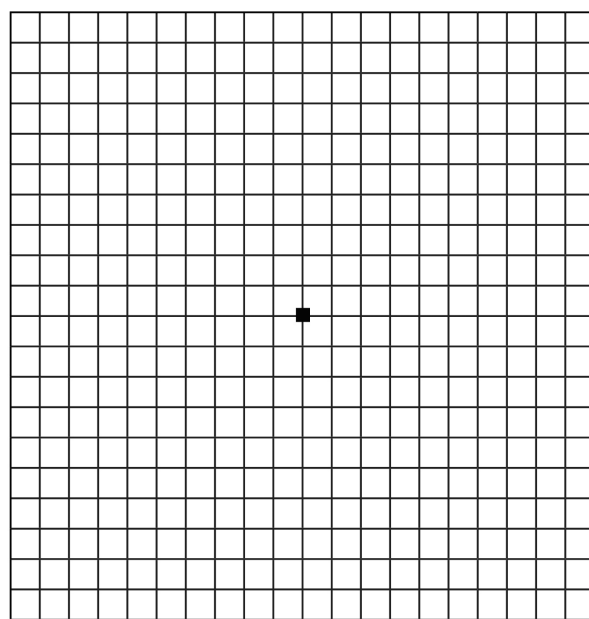
(Source: www.enhancedvision.com)
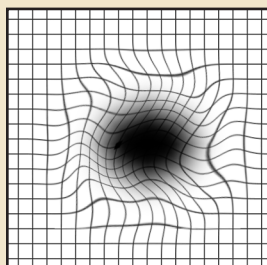
(Source: www.irregularwebcomic.net)

found more often in those patients who, because of changes in their genes, were known to have a greater chance of getting AMD in the future.

Finally, doctors also used a new, advanced tool to view individual light-sensing cells inside the eye. It is usually not easy to view individual cells in the body because of the very small size of the cells. However, being able to see single cells allows doctors to check more readily if the cells are damaged. Using the tool, doctors were able to detect damage to individual light-sensing cells that they had missed when they had used the four standard eye tests mentioned above.

To conclude, the study showed that doctors could detect the early stages of damage to light-sensing cells inside the eye by using various tools. Importantly, the advanced

tool helped doctors to be aware of eye damage that the standard tests could not detect. The study could not link the damage directly to the development of AMD because the damage did not occur more often in patients who have a higher chance getting AMD. Therefore, researchers now need to work out what are the specific types of damage to eye cells that lead to AMD.

We are grateful to you, PMRP participants, who have made this research possible. Your involvement and interest in PMRP enables us to find out more about how to prevent and treat complex diseases such as AMD. Thank you!

"Cone structure in subjects with known genetic relative risk for AMD," Megan E. Land, et al. Optometry and Vision Science 2014;91:939-949.

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.

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: Robert Haws, M.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.

eMERGE I – Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine Research Project

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 – Incorporating Research into Sight

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

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

Funding: National Human Genome Research Institute

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; Tonia Carter, Ph.D., Marshfield Clinic

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 leaders: Steven Schrodi, Ph.D., Scott Hebbring, 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.

High throughput method to assess SNP functionality in prostate cancer

Project leaders: Christopher Warren, Ph.D. and Mary Ozers, Ph.D., Illumavista Biosciences L.L.C.

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

Funding: National Cancer Institute

Many studies have found associations between prostate cancer and changes in genes. However, it is unclear how the gene changes can lead to prostate cancer. The aim of this study is to determine whether any of the gene changes disrupt the action of transcription factors, proteins that control which genes are turned on or off. The gene changes that can disrupt transcription factors might be helpful in developing drugs that can be used to treat prostate cancer.

Pharmacogenetics/ Genomics

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

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: 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.

Drug-based phenome-wide association study

Project leader: Scott Hebbring, Ph.D.

Collaborators: John Mayer, Ph.D., Zhan Ye, Ph.D., Jixia Liu, Ph.D., and Brian Hoch, Marshfield Clinic

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

The exact biologic action a drug has can be complex and not well understood. As such, some drugs can cause unexpected beneficial outcomes or even less desired adverse drug reactions. This study tries to identify these potential benefits and/or poor adverse drug reactions using the PheWAS technique in Marshfield Clinic's large patient population.

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., Baylor College of Medicine

Collaborators: Steven Schrodi, 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., Zhan Ye, Ph.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. The goal is to apply a new test to determine more accurately the size of the change in a person's FMR1 gene. The new test is especially accurate when the size of the change is small. The results of the test will help to answer the question whether persons with a small change have a FMR1 gene that does not function properly.

Th17 Activity Genome-Wide Association Study

Project leader: Steven Schrodi, Ph.D.

Collaborators: Zhan Ye, Ph.D., Donna David, Tonia Carter, Ph.D., Jennifer Meece, Ph.D., Joseph Mazza, M.D., Marshfield Clinic

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.

Development and Application of Phenome-wide Scan of Heritability (PheSH)

Project leader: Scott Hebbring, Ph.D.

Collaborators: John Mayer, Ph.D., Zhan Ye, Ph.D., Jixia Liu, Ph.D., and Brian Hoch, Marshfield Clinic

Funding: National Library of Medicine

All diseases are the result of a combination of genetic factors, also known as heritable factors, and/or environmental factors. This study is designed to measure the heritability of thousands of clinically significant diseases using multiple family structures and electronic medical records. The goal of this project is to identify genetic mutations that explain the strong heritability measurements so that genetics can be applied in "personalized medicine".

Genetic susceptibility to Staphylococcal infections

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 is looking for genes that increase a person's chances of getting Staphylococcus aureus infection.

Multi-scale analysis of influenza host-pathogen interaction: Fluomics

Project leaders: Steven Wolinsky, M.D., Jennifer Pacheco, Ph.D., and Ellie Sukerman, M.D., Northwestern University; Adolfo Garcia-Sastre, Ph.D., Mount Sinai School of Medicine

Collaborators: Murray Brilliant, Ph.D. and Peggy Peissig, Ph.D., Marshfield Clinic

Funding: National Institute of Allergy and Infectious Diseases

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. It is possible that a person's genes could be a factor in whether the influenza infection is severe or not. This study will look for changes in genes that are associated with a person's chances of getting severe influenza infection.

Genomic Postmortem Research Project

Project leader: Murray Brilliant, Ph.D.

Collaborators: 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.

Genome-wide association scan for susceptibility to a number of infectious diseases and pathogens

Project leader: Sanjay Shukla, Ph.D.

Collaborator: Steven Schrodi, Ph.D., Marshfield Clinic

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

This pilot study is designed to identify changes in genes that make it more likely that a person will become ill from infectious diseases such as Lyme disease, Ehrlichiosis, pneumonia, and Clostridium difficile infections.

NEIGHBORHOOD variables for glaucoma

Project leader: Murray Brilliant, Ph.D.

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

Funding: National Eye Institute

Primary open-angle glaucoma (POAG) is a disease that leads to blindness. The goals are to create a database with genotype information on a large number of persons with and without POAG, and to use the database to find out which genes increase a person's chances of getting POAG. (J Glaucoma 2013 Sep;22(7):517-525.)

Genomic medicine pilot study for age-related macular degeneration

Cathy McCarty, Ph.D.

Age-related macular degeneration (AMD) affects central vision, as in the picture showing an example of blurred, central vision in someone with AMD. The artist Georgia O'Keeffe went blind from her AMD and gave up painting in her later years. My grandmother developed AMD and had to give up the crocheting that she had enjoyed all her life.

With funding from the National Human Genome Research Institute, and as part of the bigger eMERGE study, we conducted a pilot study at Essentia Health in Duluth, MN. The goals of the study were three-fold: 1) to document why people do or do not participate in a study to learn their genetic risk of AMD, 2) to understand how genetic data can be stored in the electronic medical record, and 3) to document patient response to genetic testing and the behavioral changes patients make after receiving information about genetic risk of AMD.

Patients aged 50 – 65 years with a family history of AMD were recruited through their optometrist, and DNA was extracted from a blood sample. The DNA was tested for a number of genetic markers. A risk score for lifetime risk of advanced AMD was calculated using information from the genetic markers as well as knowledge about whether someone smoked, because smoking increases your risk of AMD. The optometrist provided the risk scores to patients along with counseling about personal behaviors that could help protect against the development of AMD. We called participants one to three months after they participated to ask them about their experience with genetic testing.

One-hundred and one subjects (85%) participated; 75 (74%) were female, similar to the general AMD patient population. Interviews were completed with 94 (93%) subjects. Everyone was pleased that they had genetic testing. There were mixed reactions to potential future genetic testing for other conditions and willingness to pay for genetic tests. Regardless of AMD risk score, the majority of subjects had made personal changes such as taking an antioxidant, quitting
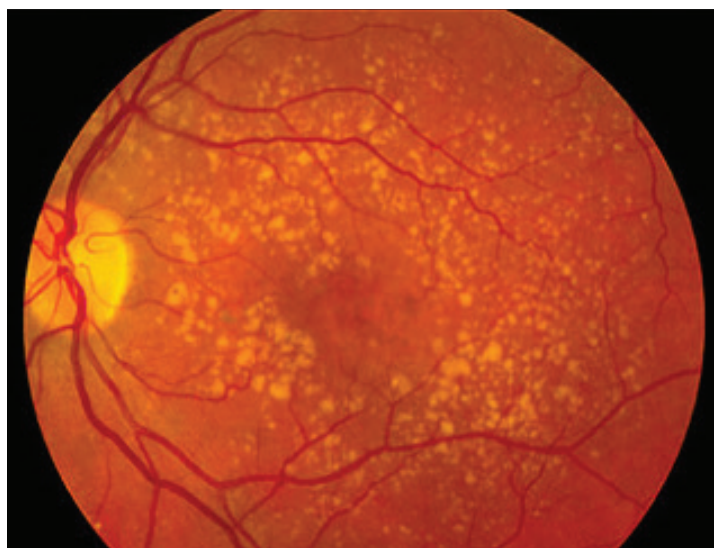
Normal Vision

Age-related Macular Degeneration
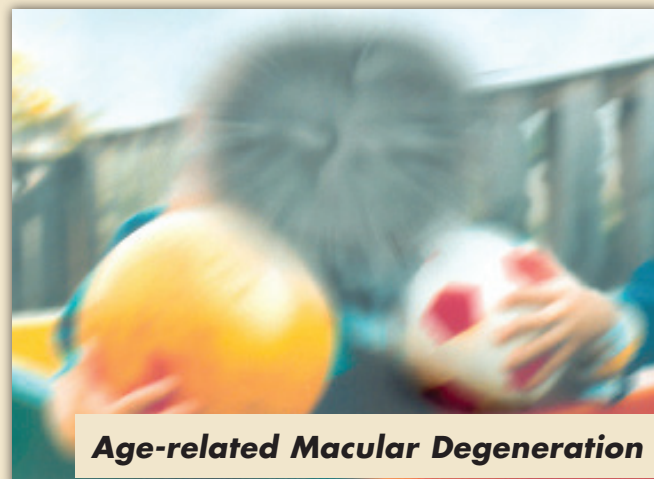
An example of normal vision and how the central area of vision is blurred or lost in someone with AMD (source: National Eye Institute)
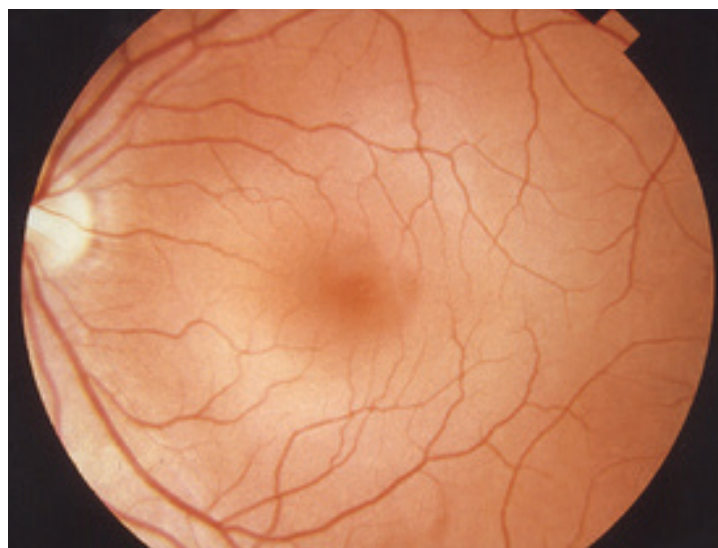
Normal eye (source: National Eye Institute)

Eye with AMD – yellow spots are deposits called drusen (source: National Eye Institute)

Age-related macular degeneration PheWAS project

Scott Hebbring, Ph.D.

Age related macular degeneration (AMD) is a genetically complex disease. Over 30 genes and more have been linked to AMD. Unfortunately, scientists continue to struggle in understanding how these genes are related to each other and how they are involved in the disease process of AMD. Many of these AMD genes have been identified by a method call the genome-wide association study (GWAS). In a GWAS, the genomes from individuals with a disease, in this case individuals with AMD, are compared to individuals without the disease. Although this technique has been effective in identifying the many genes connected to AMD, it often provides little insight into the function of the genes, how they may affect the disease process, or how to better treat or prevent the disease. In reality, the causes of human disease are frequently the result of many genes interacting with one another and the environment. As such, the same set of genes can be linked to many different diseases. To address these observations, scientists at the Marshfield Clinic are flipping the GWAS on its head using a technique called the phenome-wide association study (PheWAS).

The powerful PheWAS technique often requires a large patient population with extensive disease information, making this method ideal for the Personalized Medicine Research Project (PMRP). In PMRP, all participants are linked to Marshfield Clinic's electronic medical record system. This system allows scientists to not only identify those in PMRP who do and do not have AMD, but also those with prostate cancer, breast cancer, diabetes, arthritis, lupus, and nearly 5,000 other diseases. Whereas the GWAS technique can identify the genes that are linked to a specific disease, the PheWAS approach attempts to identify diseases that are related to a common gene or biology. As such, important knowledge about one disease can be transferred to another; this could include potential new treatment options. For example, a recent PheWAS conducted in PMRP demonstrated that multiple sclerosis, a disease of the central nervous system, and rosacea, a disease of the skin, may share a common genetic cause. Further studies are now ongoing to see if drugs used to treat rosacea can be used to treat multiple sclerosis.

To better understand AMD, 10 genes known to be involved in AMD have been studied by PheWAS using PMRP. Results indicate that these genes are not only important for the risk of AMD, but are linked to other conditions including inflammatory diseases outside of the eye. This result begins to demonstrate that 1) these genes induce an inflammatory reaction, 2) AMD is an inflammatory disease, 3) the effects of these genes are not limited to the eye, and 4) AMD may be treated or prevented with anti-inflammatory drugs. Such discoveries can only been achievable in PMRP and with Marshfield Clinic's extensive electronic medical record system. Future studies are set to better understand how these genes are involved in inflammation and to see if there are opportunities to better treat and prevent AMD.

What are inflammatory diseases?

The immune system is a network of cells, tissues and organs that work together to defend the body against infection. Inflammation is the protective reaction of the immune system to infection or injury. Inflammatory diseases occur when the immune system attacks the body's own cells or tissues causing damage to normal tissues. Inflammation is abnormal in inflammatory diseases.

Age-related macular degeneration

In later stages of AMD, research has shown that taking high doses of certain vitamins and minerals can delay AMD progression and vision loss. For wet AMD, treatments are used to stop the growth of abnormal blood vessels. However, there are no treatments that can restore vision that is already lost.

The National Eye Institute has a website that provides more information on AMD: www.nei.nih.gov/health/maculardegen/armd_facts

Genomic medicine pilot study for age-related macular degeneration

smoking, having blood lipids checked and regularly wearing sunglasses. Genetic testing for AMD was a positive experience for patients and the information encouraged people to make changes to improve their eye health. The results were so positive that the study optometrist is now working with the Essentia Health laboratory to routinely offer the AMD genetic test to appropriate patients.

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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Thank You

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