An adequate level of HDL (good) cholesterol in our blood is important for heart health. Every 1 mg/dl decrease in HDL cholesterol is associated with a 6 percent increase in cardiovascular risk, so the higher the HDL, the better.

HDL levels are highly inheritable. But the mere presence of a particular gene explains only a small fraction of the diagnosed cases of low HDL. It’s gene-gene interaction that is often the culprit causing expression of low HDL and other complex human traits, according to a recently-published genome-wide association study utilizing the PMRP database.

At the heart of the study were two large biobanks linked to electronic health records: the PMRP, linked to the Marshfield Clinic patient record; and BioVU, of Vanderbilt University Medical Center. Both biobanks are part of the National Human Genome Research Institute-funded eMERGE network (electronic Medical Records & Genomics) www.gwas.org.

Researchers used the respective electronic health records within the context of routine patient care to replicate several known associations between HDL and previously characterized genetic variants, all adjusted for age, gender, body mass index (BMI), and smoking status. By using a novel bioinformatics approach, researchers identified an association between HDL cholesterol levels and a gene that previously resisted identification in studies with larger sample sizes.

Through additional analytical strategies, researchers further identified 11 significant gene-to-gene interaction models in the PMRP cohort, eight of which showed evidence of replication in the Vanderbilt cohort.

Given this finding, perhaps more variation can be explained and new biology discovered in complex traits like HDL levels.

The study is part of a broader ongoing project, “Genome-Wide Study of Cataract and Low HDL in the Personalized Medicine.” Project leader is Cathy McCarty, Ph.D., and her external collaborators are Russell Wilke, M.D., Ph.D., and Marylyn Ritchie, Ph.D., Vanderbilt University. The project’s goal is to develop and validate electronic phenotyping algorithms to identify cases of low HDL and cataract, and to quantify the impact of two environmental factors (cigarette smoking and statin use) on those diseases.

There are two sources of HDL: your liver and the foods you eat. When too much bad (LDL) cholesterol and other substances build up, they can form artery-clogging plaque, or atherosclerosis, which narrows
I was honored to be asked to speak at a personalized medicine forum in Greifswald, Germany, in May. Investigators developing a biobank there were interested in learning about our experiences with PMRP. We hope to develop collaborations to study the impact of the environment on health outcomes when the genetics are similar, because so many people in central Wisconsin have German ancestry. To learn more, visit http://www.medizin.uni-greifswald.de/ GANI_MED/index.php?id=560&L=1.

It is with sadness that I inform you that I will be leaving Marshfield Clinic after almost 10 years. I have accepted a position as a Principal Research Scientist at Essentia Institute of Rural Health in Duluth, Minnesota. I was born and raised in Duluth and my aging parents are there. I hope to take the discoveries that we are making through PMRP and translate them into clinical care through the rural health care network of Essentia. I will continue as the Principal Investigator for eMERGE, the network of five sites involved in genome-wide association that was discussed in the May 2010 newsletter (archived newsletters are available at http://www.marshfieldclinic.org/chg/pages/default.aspx?page=chg_pmrp_newsletter). Dr. Murray Brilliant has assumed the position of Principal Investigator of PMRP. He is an experienced geneticist and a delight to work with. I know that you will give him the same support, and he will lead the project to continued success.

As always, thank you for supporting PMRP. Our success depends on you, and it has been an honor to work with you and the fantastic PMRP team these past 10 years. I wish you all well.

**From the eMERGE Principal Investigator**

Dr. McCarty will continue her close association with PMRP from her new position at the Essentia Institute of Rural Health in Duluth, Minnesota, and through the many research projects that have been so fruitful using PMRP resources. I look forward to communicating with you through this newsletter and in person regarding results of studies in progress. It is an exciting time in personalized medicine research.

In the meantime, please let me introduce myself. I relocated from the University of Arizona in Tucson and joined Marshfield Clinic almost two years ago as the James Weber Endowed Senior Research Scientist and Director of the Center for Human Genetics. I can assure you that I didn’t move to central Wisconsin for the weather (although I am finding that winter here has its charms). My wife of 33 years, Leanne, our two Shelties and I now live in Marshfield. We have one daughter, a recent law school graduate, living in Arizona.

I was at the University of Arizona for 12 years. I have held positions at the Fox Chase Cancer Center in Philadelphia and at the Jackson Laboratory in Bar Harbor, Maine. My research has involved gene discovery, including the identification of several genes associated with human genetic disorders, the effort to map and characterize our genes, and most importantly, how to determine a complex inherited trait (like hair color) from a DNA sequence. In a future column, I will detail how we are using DNA to predict who is at risk for Age-related Macular Degeneration and our efforts to prevent the disease.

**From the Director**

With humility and a deep sense of service, I assumed the role of Director of PMRP as of June 2011. This responsibility has been made easier to shoulder because of the fine work done by my predecessor, Dr. Cathy McCarty. I now share with her the privilege of working with you, the volunteers who have made PMRP one of the most valuable research assets in the world. We the stewards of this resource have the responsibility of using it wisely in research aimed at transforming “one size fits all” medical care to care that is best for you as an individual.

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**Genetic risk factor found for fibromyalgia**

Using the PMRP biobank, Jonathan Reeser, M.D., Ph.D., and his team have gained a foothold in understanding the genetics of fibromyalgia, a chronic pain syndrome that is difficult to diagnose and treat, and affects millions of people in the United States, mostly women. The study examined associations between the apolipoprotein E4 (Apo E4) allele and selected environmental exposures among a cohort diagnosed with fibromyalgia compared with control subjects. Assisting in the study was 2008 summer research intern Erin Payne, University of Michigan.

Results suggested that specific interactions between genetically susceptible individuals (those with at least one copy of the Apo E4 allele) and the environment (e.g., involvement in a motor vehicle crash) may contribute to the risk of being diagnosed with fibromyalgia. The APOE4 gene has previously been found to be associated with poor outcomes from head trauma.

Since 1964 Marshfield Clinic Research Foundation has provided hands-on research experience for undergraduate and graduate college students through summer internship programs. Successful applicants, each mentored by a research scientist, contribute to the development, data collection, analysis, and presentation of results of research projects.

This summer, three students are conducting research related to PMRP and the genome-wide association project of the electronic Medical Records & Genomics (eMERGE) Network, funded by the National Human Genome Research Institute.

• Shea Kruger, Grafton, IA, is a junior at Wartburg College in Waverly, IA, pursuing an undergraduate degree in biology. Kruger is researching cytokines, inflammatory biomarkers roles in disease, and the complex interplay of genetics with an emphasis on cardiovascular-related diseases. (Mentor: Richard Dart, M.D.)

• Tara Larson, Fairmont, MN, is a doctoral student studying nutritional sciences at South Dakota State University. Larson is assisting with grading retinal photos for diabetic retinopathy and investigating the association of a genetic marker, diet, and smoking status with diabetic retinopathy. (Mentor: Cathy McCarty, Ph.D., M.P.H.)

• Kelsey Schultz, Richfield, WI, is a graduate student at the University of Wisconsin, Milwaukee, pursuing a master’s in healthcare informatics. Schultz is working in the Biomedical Informatics Research Center on a project that will improve structured data entry into the electronic health record, making data more accessible for research. (Mentor: Luke Rasmussen)

Kruger, Larson, and Shultz are scheduled to join five other interns in giving presentations at the 2011 Summer Student Internship Program Research Symposium, August 11, in Froehlke Auditorium, Marshfield Center. The 2011 program is under the direction of Laura Coleman, Ph.D., R.D., and Bobbi Bradley, M.P.H.

The internships are made possible through the generous support of donors. For more information on the summer student program, visit http://www.marshfieldclinic.org/visitors/pages/default.aspx?page=educational_opportunities.

Advances in technology have brought about new research possibilities that could not have been fully anticipated just a few years ago. Ongoing communication to enrollees is necessary to maintain awareness and trust, especially relating to protocol changes reflecting evolving science. The PMRP gathers ongoing feedback through a Community Advisory Group (CAG) and Ethics and Security Advisory Board (ESAB), http://www.marshfieldclinic.org/chg/pages/default.aspx?page=chg_pmrp_advi_board_esab. In addition, this newsletter is used as a two-way communication tool with participants.

A study led by Cathy McCarty, Ph.D., was conducted to assess feedback. Enrollee focus groups were held, and included discussion of protocol changes to access residual blood samples. No one said that accessing stored samples would have changed their enrollment decision. For minimal-risk PMRP protocol changes, the community, CAG, and ESAB were comfortable with an opt-out model because of the initial broad consent. These results indicated that the PMRP’s multi-faceted approach to communication has been effective, and may be a model for other biobanks.


Elaine Hansen, retired nurse and wife of retired Marshfield Clinic pediatrician Raymond Hansen, M.D., speaks with Dr. McCarty at a May 2010 event celebrating the 20,000th participant to enroll in PMRP.
Gene-gene interaction influences HDL cholesterol level (continued from page 1)

the arteries and can make it more difficult for blood to flow to the heart and brain. HDL helps remove excess LDL cholesterol from the coronary arteries and delivers it to the liver where it is removed from the body. Cholesterol levels are measured in milligrams (mg) of cholesterol per deciliter (dL) of blood. Median HDL levels in the Marshfield PMRP cohort for the above-mentioned study were 45.9 mg/dl in males and 58.5 mg/dl in females. Men are considered at risk for vascular disease below 40 mg/dl, and women, below 50 mg/dl. Lifestyle changes may boost HDL levels, as well as a diet that includes whole grains, nuts, plant sterols and omega-3 fatty acids such as found in herring, salmon, sardines and flaxseed.