Personalized Medicine

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Inside

Study seeks genetic targets for drugs in treatment of obesity

About two-thirds of adults in the United States are either overweight or obese. Weight gain is increasing rapidly in children as well. Overweight patients are at higher risk for serious health problems.

Obesity develops as a result of diet and lifestyle. But studies also suggest a genetic influence. The PMRP is using its extensive database in an obesity study. The study is led by a former Marshfield Clinic researcher now at the Medical College of Wisconsin.

Russell Wilke, M.D., Ph.D., who formerly worked at the Marshfield Clinic Research Foundation Center for Human Genetics, has recently discovered that a gene called CNR1 – which affects reward-seeking behavior – can increase a patient's risk for developing obesity. Dr. Wilke's work has already shown that the CNR1 gene is associated with traits of obesity such as high body mass index, elevated cholesterol and high blood sugar.

Dr. Wilke said that variation in the CNR1 gene has also already been shown to predict cholesterol response to different diets in California. The genetic test methods used in these studies will now be tried in the PMRP population to see if they yield similar results.

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Research Foundation

From the Director

Cathy McCarty, Ph.D.

We have been very busy with research and writing grants for new research projects. The federal economic stimulus package has meant increased dollars for medical research. We are applying for a number of grants. External scientists are hoping to collaborate on projects with us. Topics include the genetic basis of adverse reactions to some antibiotics, and the genetic basis of cataracts and diabetic retinopathy, the leading cause of vision problems in working age adults. We hope in future newsletters to share good news regarding funding of these projects.

We have our first international collaboration, with scientists from Japan. We, along with Dr. Nancy Brown at Vanderbilt University in Nashville, will study the genetic basis of adverse events in people treated with ACE inhibitors for high blood pressure. De-identified DNA samples will be sent to Japan for genetic analysis.

Another first for us is a collaboration with AVIIR, a company in Palo Alto, California, that is working to develop a diagnostic test for heart attack. With appropriate approvals from our Institutional Review Board, we hope to ship de-identified serum samples to AVIIR to evaluate a number of serum markers to see how well they predict heart attack. In addition to those markers, we will assess other factors known to increase a person's risk of heart attack, such as smoking, age, gender and cholesterol levels. If successful, we have the potential to change a person's treatment to decrease their risk of a heart attack, truly "personalized medicine." Dr. Deanna Cross is leading this project. Stay tuned in a future newsletter for more information.

We welcome Sally Lang back to PMRP as our Administrative Secretary. It is great to have Sally back in the Center for Human Genetics.

PMRP enrollment is still open. We continue to collect diet history and physical activity information for subjects already enrolled. We also are asking additional questions of people who told us that they had smoked at some time in their life. Thank you in advance for completing these questionnaires! If you know anyone who is 18 years or older and lives in one of the 19 ZIP codes around Marshfield, and might like to participate in PMRP, please tell them to stop by the Lawton Center on the Marshfield campus or to call our toll free number, 1-888-334-2232 or 715-389-7733.

News in Brief

N.Y. Times features Clinic electronic records technology

The New York Times featured Marshfield Clinic's electronic health record in an article that ran December 26, 2008.

While noting that only about 17 percent of the nation's doctors use computerized patient records, reporter Steve Lohr wrote: "To visit the Marshfield Clinic, a longtime innovator in health information technology, is to glimpse medicine's digital future."

The Clinic's advanced health record is vital to PMRP research, as pointed out in the article. The Clinic "has a voluntary DNA database on nearly 20,000 people, whose health care information goes back 30 years on average – and the electronic record is the vehicle for collecting and conveying that information," the article said. "The researchers are looking for patterns in family history, lifestyle, environmental factors, lab test results and selected genetic markers that might predict the onset of conditions like diabetes and Alzheimer's disease years in advance."

Marshfield Clinic investigators contribute to international warfarin study

The International Warfarin Pharmacogenetics Consortium (IWPC) has reported in the New England Journal of Medicine results of a study to improve estimation of warfarin dose. Three Clinic investigators, using PMRP data, contributed to the study: Michael Caldwell, M.D., Ph.D.; James Burmester, Ph.D.; and Dick Berg, M.S.

Warfarin is a frequently-used anticoagulant prescribed to patients to prevent clotting. The major issue for patients who need this drug is that optimum dosage varies widely from patient to patient and is difficult to predict. If too much warfarin is used, the patient could develop bleeding problems. If too low a dose is used, complications from clotting could occur.

"Warfarin is the only oral anticoagulant currently available and we need to make it safer," Dr. Caldwell said.

Furthermore...

Targeted recruitment has started for the endometriosis project…Almost 4,000 samples from the cataract and low-HDL study were shipped for genotyping at Johns Hopkins University.

Genes may tell researchers which diabetics will respond to pills

Diabetes has reached epidemic proportions. It is the fourth-leading reason for a health care visits in the United States, and accounts for about 12 percent of all health care dollars spent each year.

In the U.S., 90 percent of diabetes cases are type 2, sometimes called "adult-onset" diabetes. Risk factors include obesity, ethnicity, inactivity and increased age.

One of the most widely prescribed drugs for the treatment of type 2 diabetes is metformin. The PMRP and two collaborating organizations are studying two genes that are believed to influence a patient's ability to utilize metformin.

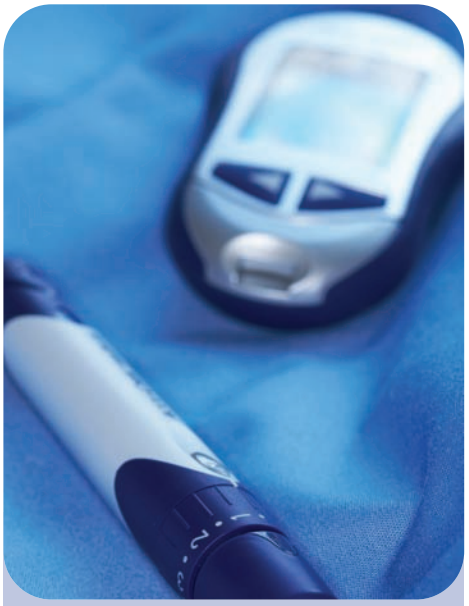
For most patients, metformin reduces high blood glucose by reducing glucose absorption from the gastrointestinal tract, reducing glucose production in the liver, and by improving the body's ability to use glucose.

But up to 30 percent of patients on metformin therapy do not respond satisfactorily and require the addition of a second drug, or stopping metformin pills and switching to treatment with insulin, which requires a shot.

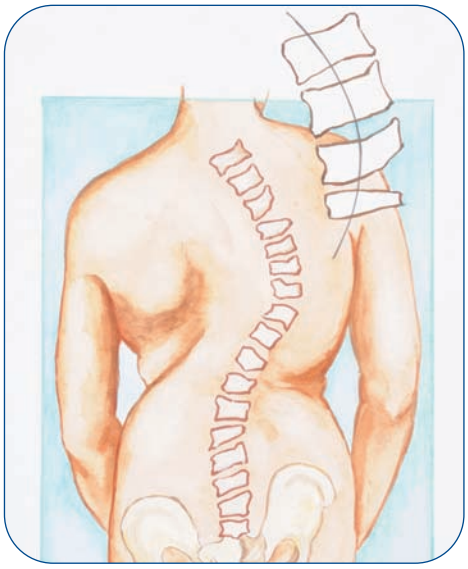
The current study involves 300 people who took metformin; 150 of them did not respond to metformin, and 150 did. Cases were drawn from the PMRP and Kaiser Permanente Georgia. Genotyping was conducted this spring at the University of California, San Francisco. Data analysis is underway. Results are expected later in 2009.

A racially diverse mix of patients will help researchers learn if the results are similar across ethnic groups. Kaiser Permanente Georgia has a patient population that is about 40 percent African American, while the PMRP population is 98 percent European Caucasian.

This is considered a "pilot" study because of its small size. The next step would be to test these gene associations in a larger sample in Marshfield Clinic, said Cathy McCarty, Ph.D., Director of the PMRP. The larger study would use a prospective design (following patients over time) and involve people who do and do not respond to metformin.



Families sought for adolescent scoliosis study



"Family Trios" consisting of a child affected with adolescent idiopathic scoliosis (AIS), and two parents available for DNA collection, are being sought for a study.

Adolescent Idiopathic Scoliosis (AIS) is a spinal curvature condition estimated to affect 2 to 3 percent of the population. AIS is often seen in multiple family members. This study will search for a gene that may increase the risk for a person to develop AIS. When this gene and other genes are identified from other groups, the data can be used to help guide treatment. It will also provide information for patients and families about the risks for AIS in other family members.

There will not be a charge to you or your insurance company for participation in this research project. There will not be compensation for time for participation in this project. Risks pertaining to this research project would be that of a blood draw.

For more information, or if you and your family are interested in participating, contact Terrie Kitchner, research coordinator, at 1-800-782-8581 ext. 79141 or 715-387-9141.

Facts about genetics

- Swiss biologist Friedrich Miescher first isolated DNA (deoxyribonucleic acid) in 1869.
- DNA is made up of chemicals, arranged in a specific order, or sequence, which make up genes. Genes are the "blueprint" for growth and development.
- Environmental factors may result in certain genes expressing or not expressing themselves. In fact, it's believed that the majority of our genes do not do anything.
- A single cell can contain six to nine feet of DNA.
- Humans share about 99 percent of the same DNA sequence.
- The only cells in the human body that do not contain DNA are red blood cells.

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Study seeks genetic targets for drugs in treatment of obesity *(continued from page 1)*

According to Dr. Wilke, the risk of becoming obese involves complex interactions between genetics, behaviors and socio-environmental factors. So the treatment of these medical problems can be equally complex. "Our research focuses on the identification of genetic markers that might eventually lead to better drugs for the treatment of obesity."

Research finds genetic association between breast cancer treatment and blood clots

Adedayo Onitilo, M.D.

Tamoxifen has been used in breast cancer treatment for more than 30 years. Some breast cancer cells require estrogen to grow, and tamoxifen prevents estrogen from binding to its receptor, thus blocking cancer growth.

Tamoxifen saves the lives of many women. Unfortunately, tamoxifen can cause fatal blood clots in certain cases.

Adedayo Onitilo, M.D., Co-Investigator on the Personalized Medicine Research Project, has completed a study that offers the first evidence identifying which genetic variations predispose an individual to tamoxifen-caused blood clots. Results were published in Breast Cancer Research and Treatment.

Dr. Onitilo studied DNA from 220 tamoxifen-treated individuals with breast cancer in the PMRP. Sixteen of them (7 percent) developed blood clots.

Although the sample is small and investigation continues, the study pushes medicine closer to the day when patients can be tested before undergoing tamoxifen therapy and, if they carry the susceptible genes, can be offered alternative treatment.

The study is a collaborative effort, and includes Russell Wilke, M.D., Ph.D., of the Medical College of Wisconsin, and a team led by David Flockhart, M.D., Ph.D., at the University of Indiana School of Medicine.

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

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