Annual Newsletter 2011

Amish Research Clinic
Of the University of Maryland
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Greetings from the Amish Research Clinic

We hope that this newsletter finds you healthy and happy. We send this newsletter to you each year to keep you informed about our new studies and what we have learned from the studies that we have completed.

Since 1995, we have enrolled over 5,000 Amish volunteers in our studies. We currently have 11 active studies. None of this could have been possible without our compassionate Amish Community.

Dr. Shuldiner and his staff are grateful to our volunteers and the Amish Community for their partnership and support. Together, our research has resulted in new discoveries and it has helped us understand the causes of a number of diseases. At the same time, it has benefited thousands of Amish volunteers by providing free medical evaluations and screenings.

Many of our studies continue to need volunteers. Volunteering provides a number of health benefits including free medical evaluations and screening for a number of common diseases and disorders. Participating in research studies also provides the opportunity to contribute to new knowledge, which may help millions of people with the diseases that we study. Some of the studies are conducted at our clinic in Lancaster and free transportation to and from the clinic is provided. Other studies are conducted right in your own home. Not only do you gain lots of knowledge about your health but with most studies, we even pay you for your time and effort.

If you have any questions or you are interested in participating in any of our studies, please call 717-392-4948. You can also write us a note. Make sure you include your address so we can get back to you.

Alan Shuldiner

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Our Mission Statement

The mission of the Amish Research Clinic is to contribute to improvements in Health Care through research. To develop and cultivate relationships with our study participants and the Amish Community in general. To serve as a resource for information and knowledge to the Amish Community.

Ongoing Studies:

The PAPI Study

The goal of this study is to understand why some people do not respond to commonly used medications to prevent heart attacks including aspirin and clopidogrel (Plavix). This 8-day study involves taking clopidogrel and aspirin and having blood samples tested to see how well the medications prevent the blood from clotting. PAPI participants also get free testing for heart problems, high cholesterol, liver, kidney, and thyroid problems, and monetary compensation for their time and effort. To date, more than 650 subjects have participated in this study.
To further explore why some people respond more than others to clopidogrel (Plavix), we invited a small number of participants into a study in which three different dosages of clopidogrel were taken over three different 8-day periods. An additional 8 day period was added in which participants took clopidogrel along with a commonly prescribed over the counter medication for the stomach, omeprazole (Prilosec), which is thought to alter how clopidogrel is handled by the body. To date 18 subjects have participated in this study which will extend the knowledge we have gained in the PAPI Study.

Salt Loading and Thiazide Intervention (SALTI) Study

Based on our exciting finding with a gene called STK39, we have initiated a new study to address (1) why some people can get rid of excess salt and water in their diets and control their blood pressure, but others develop increased blood pressure when they eat diets that have a lot of salt in them and (2) why a commonly prescribed blood pressure medication, thiazide, only works in some, but not all high blood pressure patients. We plan to recruit 120 participants in 2 years. Participants of the SALTI study will spend half a day in our clinic and take thiazide for 4 weeks. So far 74 participants have enrolled in or finished the SALTI study protocol and we want to thank everyone, including many more who expressed an interest and agreed to be screened for eligibility. We will start to analyze our data shortly and keep everyone updated on our findings. SALTI is still actively enrolling so if you would be willing to participate in this study, please contact us in writing or by telephone (717) 392-4948 at the Amish Research Clinic. You don't have to have elevated blood pressure to participate.

Amish Family Osteoporosis Study

This study was started in March 1997 and thanks to our many wonderful Amish participants, we are making great progress in studying genes that are important for bone health. We have found regions on chromosome 7 and 21and variations in a gene called EIF2AK3 that are likely to contain genes that influence bone health. This study remains active and in particular we are now studying the factors that cause some people to lose more bone after middle age while other people tend to be very slow 'bone losers". If you are interested in this study, which would involve having another measurement of your bone mineral density, please call or write to the clinic.

The Amish Family Diabetes Study Changes including Fat Biopsy

Diabetes is a very common disease in which the level of sugar in the blood is elevated. This can lead to eye, kidney, nerve, and blood vessel problems. Over the years, we have recruited more than 1,300 volunteers into this study. Recently, we tested nearly 100,000 different genetic variations in blood samples from participants of the Diabetes Study and found a new gene, called GRB10, that may be involved in diabetes. We are also working with an international team from around the world to identify additional diabetes genes. It turns out that most of the diabetes risk genes discovered in the general population are also present in the Amish. We hope these discoveries will lead to better ways to identify people at risk for diabetes and also new and more effective ways to prevent and treat diabetes. Indeed, we have initiated two new studies of how zinc and diabetes medications work (see below).

Amish Wellness Study

In early 2010, the Amish Wellness Study enrolled over 150 Amish adults, who underwent basic wellness screening including tests of cholesterol, blood sugar, thyroid, bone strength, and heart health. Blood was also collected and stored at the University of Maryland for research. This Spring, we plan to continue this study at a location near you using our new Wellness Mobile, an RV fully equipped for wellness screenings

Seasonal Affective Disorder Study

Seasonal affective disorder (SAD) affects millions of Americans and consists of seasonal changes in mood, appetite, weight, energy and motivation. While some people have mild or little changes, others have big changes. For instance winter SAD patients have low mood, low energy, gain weight, and feel sleepy through the winter. This condition is very treatable. This is the first study of SAD in the Amish. We have sent a brief SAD questionnaire in the mail and are very thankful to the nearly 1000 people who replied. We will send it once more in another season, to see if the responses to the questionnaire change with season. We will also include a one page depression questionnaire. We will then analyze the data to find out what genes are related to seasonal changes in mood.

Fat Function Study

Excess fat in the body can lead to diabetes, high cholesterol and blood fat levels, and high blood pressure, all risk factors for heart disease. However, not all people with excess fat develop these problems. This study is designed to learn how fat cells work. The study involves testing for diabetes, blood cholesterol and fat levels and taking a small piece of fat from your abdominal region. We are particularly interested in people with specific genetic make-ups. Our early studies indicate that people with a certain genetic make-up may have fat cells that do not function properly, leading to diabetes and high blood fat levels. These studies may lead to new medications to improve fat cell function to treat the medical complications of obesity.

New Studies in 2011

You may be eligible to participate in one of our new studies. Please call if you are interested in becoming a volunteer.

Zinc Insulin Pharmacogenetics Study

Based on increasing knowledge of genes that affect diabetes, we are beginning a new study that will evaluate the effect of a zinc supplement on blood sugar and insulin levels. We plan to recruit 60 participants in the next year. Participants will spend two half days in the clinic and will take a zinc supplement for 14 days. Please call 717-392-4948 if you are interested in participating in this study.

Pharmacogenetics of Insulin Secretion

The goal of this pilot study is to determine if your genes predict how your body will respond to several diabetes medications. Enrollment in the study is complete. We hope to have all of the testing done by the end of January 2011 and the analysis finished by the summer of 2011. The results will be used to design a larger study of zinc supplementation for prevention and/or treatment of diabetes

APOC*3* Study

Based on our exciting finding that about 1 in 20 Amish people carry a gene change that helps them to clear fat from their blood faster and may help prevent heart disease, we are starting a study to learn more about this gene change called *APOC3* R19X. People with this gene change make less of a substance in the body called APOC-III. The new study will help us to learn how APOC-III works and whether lowering it in other people might be a useful way to prevent heart disease. We will compare people with and without the gene change for how their fat is distributed in their bodies, how their bodies process fat, cholesterol and sugar, and how fat and cholesterol move around in their bloodstream.

Osteoporosis Pseudoglioma (OPPG) Study

OPPG is a very rare disorder of childhood brittle bones and blindness from birth. We are studying children with OPPG in the Old Order Mennonite community, using a new drug treatment that normalized the bones in mice with OPPG. In this study, we are using not only DEXA but a research tool called pQCT (done at the Children's Hospital of Philadelphia) to measure bone strength.

PPAR Study

According to some studies, a popular medication for adult diabetes, pioglitazone, does not work in about one-third of all patients to whom it is prescribed (all drugs have varying degrees of effectiveness in different people). The study that goes by the title "PPAR" (real name: Pharmacogenomics of Thiazolidinedione Response) is a new study designed to determine the genetic background for the varying degree of response to this diabetes medication. This study is currently enrolling men and women aged 35-64 years who are approximately 10-80 lbs overweight. Although the drug is used to treat diabetes, only persons WITHOUT diabetes are eligible. This study is funded by the National Institutes of Health. Persons will be taking medication for 12 weeks. Before and after the course of drugs, a small piece of fat will be removed through a hole in the skin. Compensation is offered for participation and a 10-week weight loss program is offered afterward. If you are interested in participating in this study, please contact the clinic.

New Findings in 2010

Amish Family Calcification Study and HAPI Heart Study

We discovered three genes that influence cardiovascular disease. One of these gene variants appears to increase calcium in the heart vessels by increasing levels of LDL cholesterol, and a second gene variant appears to increase calcium levels through a pathway that we don't yet understand. Finally, we have identified a third gene variant, not found in any other population but present in a small number of Amish, that appears to decrease levels of calcium in the heart vessels, possibly by decreasing levels of fats in the blood. This is a very exciting result and we are trying to understand how having this mutation seems to make you healthier. In addition, we have recently found that how much fat you have in your liver is partially under genetic control and that some, but not all, of the genes associated with liver fat are also associated with cholesterol levels in the blood.

Why some people do not respond well to clopidogrel (Plavix)

Clopidogrel is often prescribed in people to prevent heart attacks and strokes. However, it does not work in everyone. A new and exciting finding from our PAPI study is that a variation in a common gene called CYP2C19 is a major predictor of response to clopidogrel. Approximately 30% of the population carries the variation that predicts a poor response. These findings and similar findings of others lead to an FDA mandated change in the drug's label. This is an important finding because people with this variation might benefit more from a different medication to prevent heart attacks.

Discovery through collaboration

This year we worked with a large number of research groups around the world, contributing information from the HAPI Heart Study and other Amish studies, to discover variations in genes that influence blood sugar, cholesterol and fat levels, height, kidney and thyroid function, fat in the liver, and other traits related to health and disease.

Genes related to blood level of vitamin D

This year, in collaboration with about a dozen other researcher groups in the US and other countries, we found an association of blood vitamin D level with 4 genes. About 30% of one's vitamin D level is controlled by genes. This is one of the reasons that some people need more vitamin D to maintain a normal blood level than others.

New gene related to osteoporosis

We have found a new association of a gene called fibroblast growth factor with bone strength. We expect that there are likely a couple dozen genes that are important for bone health.

Women's Breast Health Study

Mammographic breast density refers to the amount of dense tissue – meaning glands and ligaments – in the breast and can be measured by a routine mammogram (or x-ray of the breast to detect unsuspected cancer). Studies have repeatedly shown that women who have high breast density are more likely to develop breast cancer. Yet no one knows exactly why this is so. What we do know is that breast density (like breast cancer) is influenced by both genetic and non-genetic factors. The primary goal of this study is to identify the genes that influence breast density, which may improve our understanding of breast cancer.

Between June of 2005 and December of 2010, nearly 1,500 Amish women had a free mammogram and provided blood samples so that we could begin searching for the genes that influence breast density. So far we've discovered that at least one gene, *ZNF365*, which has been recently associated with susceptibility to breast cancer and breast density in other populations, is also associated breast density in the Amish. This finding was based on studying only a few dozen of the ~20,000 known protein-coding genes in a small subset of women, so we hope to identify many new genes over the coming year as we expand our search.

In the mean time, we would like to remind all women of the importance of getting a routine mammogram. For example, the National Cancer Institute recommends that women over the age of 40 years have a mammogram every 1-2 years coupled with a breast exam by a doctor to improve the early detection of breast cancer. By doing so, a woman may reduce her risk of dying from breast cancer by about 17% (if she is 40 to 49 years old) and by about 30% (if she is 50 years or older). If you need assistance scheduling a mammogram, please call us at 717-392-4948.

2010 Publications

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