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Amish Research Clinic Annual Newsletter 2013

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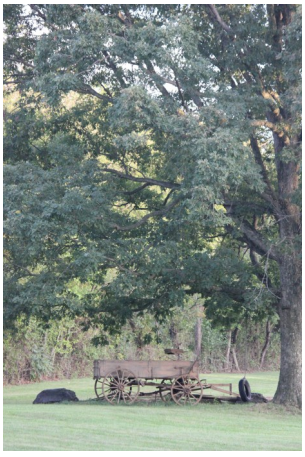
Greetings from the Amish Research Clinic

It's hard to believe that we have been at our Greenfield location for 6 years and we have been doing research at the Amish Research Clinic for 18 years. Some of the diseases we have studied include diabetes, osteoporosis, high blood pressure, cholesterol abnormalities, breast density, celiac disease, longevity, seasonal affective disorder, obesity, heart disease and wellness.

In this newsletter, we provide updates on the progress of our research and information on new studies. Several of these studies continue to enroll volunteers. For most of these studies, you do not need to have the disorder to participate.

Volunteering provides a number of health benefits including free medical evaluations and screening for a number of common diseases and disorders. It also provides the opportunity to contribute to new knowledge, which may help millions of people with the diseases 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. In most of the studies, we even pay you for your time and effort. If you are interested in participating in any of our studies, please call 717-392-4948 or write to learn more. Please give us your contact information.

In addition, your participation will one day lead to the genetic discoveries that will pave the way to new preventions, treatments, and even cures for these common disorders. We look forward to serving the Amish community for years to come and wish you and your family health and happiness in 2013.



Our Mission Statement

The Amish Research Clinic contributes to improvements in healthcare through research. We serve as a resource for health information and knowledge to the Amish Community.

Volunteering provides a number of benefits

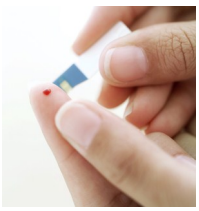
Ongoing Studies

The Amish Family Diabetes Study (active)

Diabetes is a very common disease caused by increased sugar in the blood. It is on the rise world wide , especially in the United States, Asia and India. Symptoms of diabetes may include fatigue, increased thirst, hunger and urination. If left untreated, diabetes can lead to eye, liver, kidney, nerve and blood vessel problems. There are two major types of Diabetes. **Type 1** occurs in children and the only treatment is insulin since the body cannot make its own. **Type 2** diabetes is more common and generally occurs in overweight adults. Diet, weight loss, pills and sometimes insulin injections are needed to keep the blood sugar under control.

Thanks to many of the Lancaster Amish , we have recruited over 1300 volunteers and tested nearly 100,000 different genetic variations in participants of the Diabetes Study. One of the genes we identified in the Amish that is involved in type 2 diabetes, called GRB10 appears to also be important in other populations around the world.

Since Type 2 diabetes tends to run in families, we continue to study which genes are involved in the development of Type 2 diabetes so that we can better identify people at risk for diabetes and also find new ways to prevent and treat it. If you or someone in your family is experiencing the above symptoms and would like to be tested for Type 2 diabetes, please call the clinic at 717-392-4948. All testing is free and usually done in your home.



Zinc Pharmacogenetics Study (inactive)

Based on increasing knowledge of genes that affect diabetes, we enrolled 60 participants in a study to evaluate the effect of a zinc supplement on blood sugar and insulin levels. The participants spent two mornings in the clinic and took a zinc supplement for 14 days in between.

Recruitment for this pilot study is completed. The next step is to analyze all of the information that was gathered in the study. The early results are promising, and we hope that this will lead to a larger study of zinc in the future.

We evaluated the effect of a zinc supplement on blood sugar and Insulin levels.

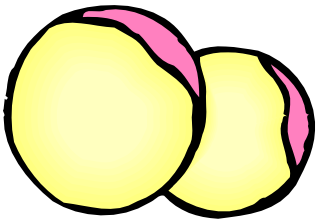
UCP2 Study (active)

The goal of this study is to identify how certain genes influence response to atenolol, a medicine used to treat high blood pressure, in people who have type 2 diabetes or pre-diabetes. In addition to its effects on blood pressure, we are also interested in atenolol's effects on cholesterol and blood sugar. We are enrolling people with type 2 diabetes or pre-diabetes who are not treated with insulin and who do not have heart disease. The study is approximately 10 weeks long and involves a test to see how sensitive the body is to sugar and insulin, a fat sample, and an ultrasound of the heart before and after 8 weeks of treatment with atenolol. We will be continuing to enroll participants over the next 6 months.

We serve as a resource for health information and knowledge to the Amish Community

Ongoing Studies cont.

MiACT Study - Metabolic Impact of ApoC-III (active)



Fat Cells

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 have started 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 is helping us to learn how ApoC-III works and whether lowering it in other people might be a useful way to prevent heart disease. We are comparing 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. So far, over 50 people have enrolled in the study, which is funded by the National Institutes of Health.

Wellness Study (active)

The Amish Wellness Study continues to recruit participants. This study offers all Amish adults basic wellness screening including tests of cholesterol, blood sugar, thyroid, bone strength, and heart health. Blood is also being collected and stored at the University of Maryland for research on genetic and non-genetic factors in health and disease. The research team hopes to visit all Amish households.

Testing takes place in our "Wellmobile" housed in a large motor vehicle which visits each Church district. If we haven't visited your Church district yet, we will be there in the future. To date, over 1300 Amish individuals ages 18 and older have enrolled in the Wellness Study, which is funded by the University of Maryland Program in Personalized and Genomic Medicine. Thank you!

The wellness study provides comprehensive testing to all adult participants at no cost.

Breast Density Study (inactive)

Mammographic breast density refers to the amount of dense tissue —meaning glands and ligaments — in the breast. It 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. 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 several genes that are associated with breast density in the Amish. At least one of these genes is also associated with susceptibility to breast cancer and breast density in other populations. We plan to confirm and extend our findings by working with other researchers in the US and abroad over the coming year. In the meantime, 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.

PPAR Study (inactive)

This study is no longer taking in participants. We thank the around 30 people who participated at the Amish Research Clinic. The purpose of the study was to determine why some people do not respond to pioglitazone, a drug used to treat diabetes. Participants took the drug for 12 weeks. We are now in the process of analyzing all the samples to find the genes responsible for individual differences in response. We have run some of the tests we had planned on the samples. We will finish the analyses this year and come back with more information in next year's newsletter.

Ongoing Studies cont.

Salt Loading and Thiazide Intervention (inactive)

Based on our exciting finding of a gene called STK39, we are studying (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. Participants of the SALTI study spent half a day in our clinic and took thiazide for 4 weeks. The study has completed the recruitment phase and w e successfully recruited 125 subjects, therefore this study is currently inactive. We have started to analyze our data and will keep everyone updated on our findings. We would like to thank everyone that completed the study, including many more that expressed an interest and agreed to be screened for eligibility.

Seasonal Affective Disorder Study (inactive)

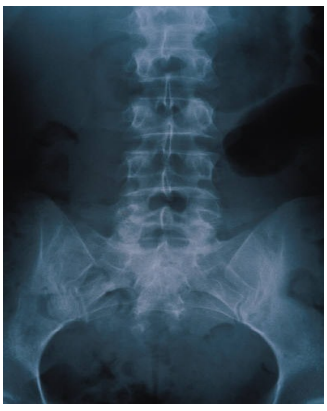
Seasonal affective disorder (SAD) affects millions of Americans. People with SAD have low mood, low energy, gain weight, and feel sleepy through the winter. Decreased day length triggers SAD in some individuals and light therapy treats SAD. Some patients need medications or talk therapy for a full improvement. This is the first study of SAD in the Amish. The manuscript on the frequency of SAD and heritability of the disorder, both lower than expected, has been published in the Journal of Affective Disorders . We have also published an article on validating the questionnaire we used in the Amish. The genetic analysis of SAD in collaboration with Australian researchers did not identify any genetic marker for SAD. It is more likely that SAD is a result of the environment than of genes, and it is interesting to identify the factors that may protect many Amish from SD. We will be working on obtaining a grant to be able to study actual patients with SAD in the clinic in greater detail in the following years, to find out how we can predict who will better respond to light treatment. In the meantime, patients who experience problems with SAD or depression can call the clinic for a list of referrals to mental health professionals in the area.

PAPI Study (inactive)

The goal of this study is to understand why some people do not respond to medications used commonly to prevent heart attacks, aspirin and clopidogrel (Plavix). In this 8-day study, participants took clopidogrel and aspirin and had blood samples tested to see how well the medications prevent the blood from clotting. PAPI participants also received free testing for heart problems, high cholesterol, liver, kidney, and thyroid problems, and compensation for their time and effort. More than 650 subjects have participated in this study. Searching the genome, we found a gene called CYP2C19 that is an important determinant of response to clopidogrel. The test is now being used to better treat people with heart disease, who have received stents. To further explore why some people respond more than others to clopidogrel (Plavix), we invited eighteen participants into a study in which three different dosages of clopidogrel were taken over three different 8-day periods. This study showed that a higher dose of clopidogrel may be used in some patients with resistance to the usual dose of clopidogrel. We have also found an interesting gene that predicts response to aspirin called *PEAR1*. A new study, beginning in 2013 will study this gene further.

Osteoporosis Study (active)

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 21 and variations in a gene called EIF2AK3, that are likely to 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 have participated in the Wellness Study and your heel study indicated you may need further testing, you may call the clinic to arrange an appointment for a dexascan. The dexascan will be performed free of charge as part of the Osteoporosis Study.



Osteoporosis Pseudoglioma (OPPG) Study

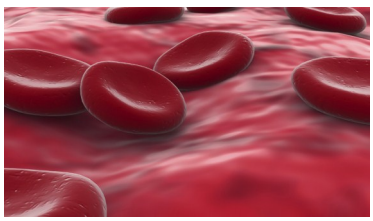
Osteoporosis pseudoglioma syndrome (OPPG) is a rare genetic disorder of weak bones (osteoporosis), blindness (from birth) and sometimes behavioral problems. Although OPPG is extremely rare in the general population (about 60 people with OPPG are known worldwide), many children with OPPG have been diagnosed in the Old Order Mennonite community in PA (13 children so far). OPPG can lead to multiple broken bones (fractures) of the upper and lower leg bones and back. Dr Streeten has been studying OPPG for over 10 years, trying to find a new treatment that will help strengthen the bones in people with OPPG. Traditional medications used to treat osteoporosis can help in OPPG but do not totally prevent fractures. We completed a 6 month study of lithium, which was shown to strengthen the bones of mice with OPPG and it did strengthen the bones in children with OPPG but worsened behavioral problems in those who had behavior problems at baseline. We are now studying the quality of bones in OPPG with a special type of x-ray called pQCT, a painless procedure which gives detailed pictures of the bones to help us understand why the bones are so fragile in OPPG.

Some of the diseases we have studied include diabetes, osteoporosis, high blood pressure, cholesterol abnormalities, breast density, celiac disease, longevity, seasonal affective disorder, obesity and heart disease.

New Studies

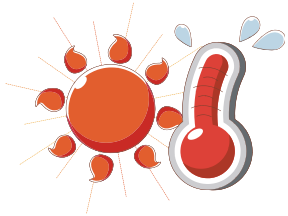
PEAR1 Study

Heart disease is the leading cause of death in the United States with heart attacks being the most common form of this disease. A heart attack occurs when a blood vessel becomes blocked preventing blood from reaching the heart. When a person has a heart attack, aspirin is the most commonly given drug to help patients get better. Aspirin works by preventing cells in the blood called platelets from sticking together and forming clots, which reduces the risk of heart attacks. While aspirin prevents blood clots from forming in many people, some people do not respond as well. This is known as aspirin resistance. One person may need a different dose of aspirin than another person to effectively prevent blood clotting. Some of these differences are due to differences in age, sex, and medical conditions. The purpose of this study is to examine the effect of variations in the ***PEAR1*** gene on a person's response to aspirin. Specifically, we will test whether increasing the dose of aspirin increases the anti-clotting effect in people with variations in *PEAR1*. You may be contacted if you have previously participated in our research studies and have agreed to be re-contacted for new studies for which you may qualify or if you are related to someone who has participated in a study at the Amish Research Clinic.



Genetics of Pain Study

Pain is the primary reason that patients seek medical attention. Recent medical advances have dramatically increased life expectancy and, therefore, the number of people living with chronic diseases and chronic pain. More than 116 million Americans are chronically in pain, and they make more than 70 million visits to healthcare providers at a cost of more than $600 billion every year. Most of the patients have their pain for five or more years, causing decreased quality of life and increased stress for the entire family. Scientists believe that there is a link between our genes and how we sense pain, which is why some people require more pain medication than others after the same injury or develop chronic pain after recovering from an illness. However, exactly which genes are involved in determining these differences are not known. The goal of this research project is to gain a better understanding of how our genes control pain sensing and why some people feel more pain. We plan to recruit 100 participants and measure their response to pain from heat, cold and pressure. While the participants will experience some temporary pain from heat, cold and pressure produced by an instrument placed on their arms, they will not be injured in any way. The study will require around 3 hours and participants will be compensated for their time and effort. If you are interested, please call our clinic @ 717-392-4948 and find out more information



Amish Imaging and Mental Illness Study

We are starting a new study to learn more about mental health problems in the Amish community. We would also like to find out more about brain differences that make it more likely someone will have mental health problems. This study has two parts. The first part involves completing a brief survey that asks about feelings and behaviors. We will mail this survey to your home. For the second part of the study, participants will travel by van in small groups to Baltimore, MD. In Baltimore, participants will complete other study tasks and tests. We will use a method that takes pictures of your brain; this is called magnetic resonance imaging (MRI). We can use these pictures to understand the brain circuits, or wirings, which are related to mental health. These brain wirings are often heritable, meaning that they run in families. The study tasks in Baltimore, MD will take about six hours to complete. The van ride takes about two hours each way, so you would be gone for about 10 hours. Study participants will be compensated for their time and effort. Amish adults and children aged 12 – 62 years old are eligible to participate. We will be enrolling persons with and without histories of mental health problems.

If you would like to learn more about this study, please contact the Amish Research Clinic at (717-392-4948).

Our Amish Research Clinic Staff

Front row: Sylvia Newcomer, Yvonne Rohrer, Donna Trubiano
Back row: Patrick Donnelly, Theresa Roomet, Elizabeth Zehr,
Mary Morrissey, Maryann Drolet, Susan Shaub and Nancy Weitzel

Publications for 2012

1. Living the good life? Mortality and hospital utilization patterns in the old order amish.PLoS One. 2012;7(12):e51560. doi: 10.1371/journal.pone.0051560. Epub 2012 Dec 19.
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4. Seventy-five genetic loci influencing the human red blood cell.Nature. 2012 Dec 20;492(7429):369-75. doi: 10.1038/nature11677. Epub 2012 Dec 5.
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6. The functional G143E variant of carboxylesterase 1 is associated with increased clopidogrel active metabolite levels and greater clopidogrel response.Pharmacogenet Genomics. 2013 Jan;23(1):1-8.
7. Comparison of BMI and Physical Activity Between Old Order Amish Children and Non-Amish Children.Diabetes Care. 2012 Oct 23. [Epub ahead of print]
8. Large-scale gene-centric meta-analysis across 32 studies identifies multiple lipid loci.Am J Hum Genet. 2012 Nov 2;91(5):823-38. doi: 10.1016/j.ajhg.2012.08.032. Epub 2012 Oct 11.
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15. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways.Nat Genet. 2012 Sep;44(9):991-1005. doi: 10.1038/ng.2385. Epub 2012 Aug 12.
16. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes.Nat Genet. 2012 Sep;44(9):981-90. doi: 10.1038/ng.2383. Epub 2012 Aug 12.
17. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations.Nat Genet. 2012 Jul 15;44(8):904-9. doi: 10.1038/ng.2352.
18. The C allele of ATM rs11212617 does not associate with metformin response in the Diabetes Prevention Program.Diabetes Care. 2012 Sep;35(9):1864-7. Epub 2012 Jun 29
19. Impact of common variation in bone-related genes on type 2 diabetes and related traits.Diabetes. 2012 Aug;61(8):2176-86. Epub 2012 Jun 14.
20. Genome-wide association for abdominal subcutaneous and visceral adipose reveals a novel locus for visceral fat in women.PLoS Genet. 2012;8(5):e1002695. doi: 10.1371/journal.pgen.1002695. Epub 2012 May 10.
21. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance.Nat Genet. 2012 May 13;44(6):659-69. doi: 10.1038/ng.2274.
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23. Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture.Nat Genet. 2012 Apr 15;44(5):491-501. doi: 10.1038/ng.2249.
24. CYP2C19 genotype and cardiovascular events.JAMA. 2012 Apr 11;307(14):1482; author reply 1484-5. doi: 10.1001/jama.2012.443. No abstract available.
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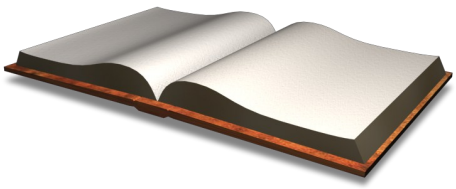

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