



## Winter Newsletter 2010



**Amish Research Clinic  
Of the University of Maryland  
1861 William Penn Way  
Lancaster, PA 17601  
717-392-4948**

### **Greetings from the Amish Research Clinic.**



This year marks our 15<sup>th</sup> Anniversary!

We have enrolled nearly 5,000 Amish volunteers in our studies. We currently have 10 active studies. None of this could have been possible without our compassionate Amish Community.

Dr. Shuldiner and his staff would like to take this opportunity to thank all 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 not only in the Amish, but in all human populations. At the same time, it has benefited thousands of Amish volunteers by providing free medical evaluations and screenings.

The purpose of this newsletter is to provide updates on the progress of our research. Many of these 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.

### *Our Staff*

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## **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. This study is still open to enrollment. If you are interested in participating, please call or write.

### **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 21 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**

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. 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.

## **New Studies in 2010**

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

### **Salt Loading and Thiazide Intervention (SALTI) Study**

Based on our exciting finding with STK39, we have initiated a new study to address (1) why some people can get rid of excess salt and water and control their blood pressure, but other people have high blood pressure and need to be medicated to control their blood pressure; 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. 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 Wellness Study**

A new study called the Amish Wellness Study has started. This study will offer all Amish adult's basic wellness screening including tests of cholesterol, blood sugar, thyroid, bone strength, and heart health. Blood will also be collected and stored at the University of Maryland for research. The research team hopes to visit all Amish households by Church district. The testing will take place in a "Mobile Wellness Clinic" housed in a large motor vehicle which will come to you.





## **Meanwhile in the laboratory.....**

### **Amish Family Calcification Study**

Many thanks to the more than 1,000 people who have participated in the Amish Family Calcification Study. In the Amish, as in other populations, the amount of LDL (“bad”) cholesterol in the blood is correlated with the amount of calcium in the blood vessels of the heart. By analyzing DNA isolated from the blood, we have now identified several gene variants that are also associated with how much calcium people have in the blood vessels of the heart. Additionally, we are now taking a more detailed look at the images of the heart and measuring the amount of fat in the liver and around the heart. Everyone has some fat in these areas, and we want to see if the amount of fat at these sites is related to other bad outcomes, like how much calcification you have in the arteries, and/or your risk or diabetes.

### **Amish Staph Study Findings**

Staph is a bacteria or germ commonly found in the nose. The vast majority of people who carry the Staph bacteria in their nose remain infection-free; however, Staph can cause a skin infection if it gets into a cut. This study examined how common Staph is in the Amish, and if related people are more likely to have Staph bacteria in their nose. Thank you to the 400 participants who have enrolled in the Amish Staph Study. We have found that about one in five participants had the Staph bacteria in their nose which is similar to what is seen in other communities. People who were related to someone with Staph in their nose were not more likely to have Staph in their nose than the rest of the community. This is important because it means that people’s genes are not what determine whether they have Staph in their nose. We are exposed to Staph and other germs (like cold viruses) in our everyday environment. We don’t routinely recommend treatment for Staph in the nose but you can take steps to reduce your risk of infection whether Staph is in your nose or not. Any opening in your skin increases the risk of infection. Keep your cuts and scrapes: Clean, Dry and Covered. Washing your hands with soap and water is one of the best ways to prevent diseases.

### **Amish Sunshine Study**

We have completed a small study, “The Sunshine Study” in which we are evaluating differences in how well people make Vitamin D in their bodies after a sunlamp exposure to the skin. We plan to continue the Sunshine Study after we get additional research funding to support it.

### **The Sitosterol Study**

The study seeks to understand how levels of plant sterols in the blood differ between participants with one or zero copies of an altered sterol transporter gene. To date over 300 Amish volunteers have provided blood samples. Our findings suggest that the individuals with one copy of the changed sterol transporter are not at increased risk for heart disease. We are near completion of a new phase of this project in which we are looking at how plant sterols in the diet affect health. To date 12 Amish volunteers have participated in the new phase.

### **Flu Vaccine Study**

Older people are especially susceptible to getting the flu and are at greater risk of hospitalization and dying when they get it. The flu vaccine is the best way to prevent the flu. However, it is less effective in older people. The new Flu Vaccine Study aims to find out why some older people respond well to the flu vaccine while others do not. The study involves giving the flu shot to Amish people over the age of 65 and drawing a blood sample before and after the shot to measure the response. Volunteers will receive the same flu shot that is recommended to all older people at no charge.

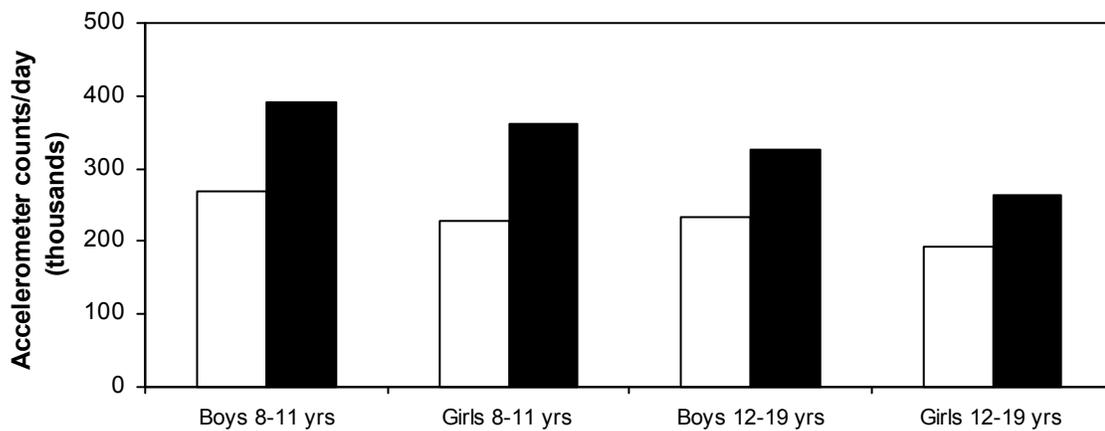




### Amish Children's Physical Activity Study

We have compared physical activity as measured in the Amish Children's Study with physical activity in a group of children from the Eastern Shore of Maryland, who are not Amish but live in a similar rural setting. For these studies we used accelerometers, a type of device worn on the hip to measure physical activity over a week. We found that Amish children are generally more active than Eastern Shore children; especially in the youngest age group we studied (see the figure below). We also found that Amish children were less frequently overweight than Eastern Shore children. It is not healthy for children (or adults) to be overweight. This study suggests that Eastern Shore children should be more physically active, like the Amish children, so they can stay slim and healthy.

Physical activity levels (accelerometer counts) in Maryland Eastern Shore (white bars) and Lancaster Old Order Amish (black bars) children.



### Women's Breast Health Study

The goal of this study is to identify the genes that influence the makeup of the female breast. The density of the breast is determined by how much gland tissue and fatty tissue is present. Increased breast density is a strong but poorly understood breast cancer risk factor. Identifying the genes that influence breast density may provide important insights into the prevention and treatment of breast cancer. More than 1,500 Amish women participated in this study. This study may improve our understanding of how genes contribute to breast density, an important risk factor for breast cancer.





### **The HAPI Heart Study**

This study was designed to better understand how genes interact with common lifestyle factors like stress and diet to contribute to heart disease. It was very successful – nearly 900 Amish community members volunteered for this study. We continue to analyze all of the information we accumulated and have made a number of very exciting discoveries. For example, we determined that the obesity-promoting effects of the FTO gene can be over-ridden by high levels of physical activity. This finding has important implications since it suggests that even if a person is born with genetic susceptibility to obesity, a healthy lifestyle can be very beneficial. These discoveries will lead to new approaches to improve health and prevent disease in the Amish and other populations as well.

## **New Findings in 2009**

### **Amish Family Calcification Study**

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 makes you healthier.

As part of the **HAPI Heart Study** and the **Amish Family Calcification 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 makes you healthier.

### **The Amish Hypertension Study**

Hypertension or high blood pressure is a common disorder that predisposes people to heart and kidney disease and stroke. Results from both the Amish Family Diabetes Study and the HAPI study show that a gene on chromosome 2 called STK39 is important in regulating blood pressure. This gene affects the amount of salt in the urine. This new finding may help us better understand how the body regulates blood pressure and may provide new targets for the treatment of high blood pressure. The unique characteristics of the Amish were instrumental in helping us identify this gene. We continue to look for additional genes that regulate blood pressure and to understand how these genes interact with other factors including diet, activity, tobacco use and stress. We continue to work with other groups around the world to discover a number of new genes. Working together with other groups allows us to discover things that none of us could discover alone.

### **A new gene for high blood pressure**

Hypertension or high blood pressure is a common disorder that predisposes people to heart and kidney disease and stroke. Results from both the Amish Family Diabetes Study and the HAPI Study show that a gene on chromosome 2 called STK39 is important in regulating blood pressure. This gene affects how our bodies eliminate salt. The results are also relevant to non-Amish populations. This new finding may help us better understand how the body regulates blood pressure and may provide new approaches for the treatment of high blood pressure.





### **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. This is an important finding because people with this variation might benefit more from a different medication to prevent heart attacks.

### **New genes for high cholesterol and sugar levels**

We have worked with other groups around the world to discover a number of new genes for cholesterol and sugar levels in the blood. Working together with other groups allows us to discover things that none of us alone could have. It is also fun!

### **Scientific Publications of 2009**

1. Shen H., Kim J.D., Subramanya A.R., Steinle N.I., Parsa A., Ober C.C., Welling P.A., Chakravarti A., Weder A.B., Cooper R.S., Mitchell B.D., Shuldiner A.R., Chang Wang Y., McArdle P.F., Wade J.B., O'Connell J., Dorff S.E., Shar S.J., Shi X., Pan L., Rampersaud E., Y.-P.C. Whole-genome association study identifies *STK39* as a novel hypertension susceptibility gene (2009) *Proc. Natl. Acad. Sci. USA* **106**, 226-231.
2. Michos E.D., Streeten E.A., Ryan K.A., Rampersaud E., Peyser P.A., Bielak L.F., Shuldiner A.R., Mitchell B.D., Post W. Serum 25-hydroxyvitamin D levels are not associated with subclinical vascular disease or C-reactive protein (CRP) in the Old Order Amish (2009) *Calcif. Tissue Internat.* [Epub ahead of print]
3. Perry J.R., Stolk L., Franceschini N., Lunetta K.L., Zhai G., McArdle P.F., Smith A.V., Aspelund T., Bandinelli S., Boerwinkle E., Cherkas L., Eiriksdottir G., Estrada K., Ferrucci L., Folsom A.R., Garcia M., Gudnason V., Hofman A., Karasik D., Kiel D.P., Launer L.J., van Meurs J., Nalls M.A., Rivadeneira F., Shuldiner A.R., Singleton A., Soranzo N., Tanaka T., Visser J.A., Weedon M.N., Wilson S.G., Zhuang V., Streeten E.A., Harris T.B., Murray A., Spector T.D., Demerath E.W., Uitterlinden A.G., Murabito J.M. Meta-analysis of genome-wide association data identifies two loci influencing age at menarche (2009) *Nat. Genet.* 2009 May 17. [Epub ahead of print].
4. Cheng Y.-C., Kao W.-H.L., Mitchell B.D., O'Connell J.R., Shen H., McArdle P.F., Gibson Q., Ryan K.A., Shuldiner A.R., Pollin T.I. Genome-wide association scan identifies variants near matrix metalloproteinase (MMP) genes on chromosome 11q21-22 strongly associated with serum MMP-1 levels. (2009) *Circ. Cardiovasc. Genet.* **2**, 329-237. PMID: 20031604
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6. Bielak L.F., Horenstein R.B., Ryan K.A., Sheedy P.F. II, Rumberger J.A., Post W.S., Mitchell B.D., Shuldiner A.R., Peyser P.A. CD34+ cell count is associated with extent of subclinical atherosclerosis in asymptomatic Amish men, independent of 10-year Framingham risk, *in press*.
7. Sanna S., Busonero F., Maschio A., McArdle P.F., Usala G., Dei M., Lai S., Mulas A., Grazia M., Piras G., Perseu L., Masala M., Marongiu M., Crisponi L., Naitza S., Galanello R., Abecasis G.R., Shuldiner A.R., Schlessinger D., Cao A., Uda M. Common variants in the SLCO1B3 locus are associated with bilirubin levels and unconjugated hyperbilirubinemia (2009) *Hum. Mol. Genet.* **18**, 2711-8.
8. Shen H., Herzog W., Drolet M. Pakyz R., Newcomer S., Sack P., Karon H., Ryan K.A., Zhao Y., Shi X., Mitchell B.D., Shuldiner A.R. Aspirin resistance in healthy drug-naïve men versus women (From the Heredity and Phenotype Intervention [HAPI] Heart Study)(2009) *Am. J. Cardiol.*, **104**, 606-612.
9. Shen H., Pollin T.I., Damcott C.M., McLenithan J.C., Mitchell B.D., Shuldiner A.R. Glucokinase regulatory protein (GCKR) gene polymorphism affects postprandial lipemic response to a dietary intervention study (2009) *Hum. Genet.* **126**, 567-74.
10. Heard-Costa N.L., Zillikens M.C., Monda K.L., Johansson A., Harris T.B., Fu M., Haritunians T., Feitosa M.F., Aspelund T., Eiriksdottir G., Garcia M., Launer, L.J., Smith A.V., Mitchell B.D., McArdle P.F., Shuldiner A.R., Bielinski S.J.,

- Boerwinkle E., Brancati F., Demerath E.W., Pankow J.S., Arnold A.M., Chen Y-D.I, Glazer N.L., McKnight B., Psaty B.M., Rotter J.I., Amin N., Campbell H., Gyllensten U., Pattaro C., Pramstaller P.P., Rudan I., Struchalin M., Vitart V., Gao X., Kraja A., Province M.A., Zhang Q., Atwood L.D., Dupuis J., Hirschhorn J.N., Jaquish C.E., O'Donnell C.J., Vasan R.S., White C.C., Aulchenko Y.S., Estrada K., Hofman A., Rivadeneira F., Uitterlinden A.G., Witteman J.C.M., Oostra B.A., Kaplan R.C., Gudnason V., O'Connell J.R., Borecki I.B., van Duijn C.M., Cupples L.A., Fox C.S., North K.E. *NRXN3* is a Novel Locus for Waist Circumference: A Genome-wide Association Study from the CHARGE Consortium (2009) *PLOS Genetics*. Jun;5(6):e1000539. Epub 2009 Jun 26.
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  13. Van Hout C.V., Levin A.M., Rampersaud E., Shen H., O'Connell J.R., Mitchell B.D., Shuldiner A.R., Douglas J.A. Extent and distribution of linkage disequilibrium in the Old Order Amish. *Genet. Epidemiol.* 2009 Aug 20.
  14. Tarasov K.V., Sanna S., Scuteri A., Strait J.B., Orrù M., Parsa A., Lin P.I., Maschio A., Lai S., Piras M.G., Masala M., Tanaka T., Post W., O'Connell J.R., Schlessinger D., Cao A., Nagaraja R., Mitchell B.D., Abecasis G.R., Shuldiner A.R., Uda M., Lakatta E.G., Najjar S.S. COL4A1 is associated with arterial stiffness by genome-wide association scan (2009) *Circ Cardiovasc. Genet.* **2**, 151-8. PMID: 20031579
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