2019 Annual Newsletter

Amish Research Clinic

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Greetings from the Amish Research Clinic

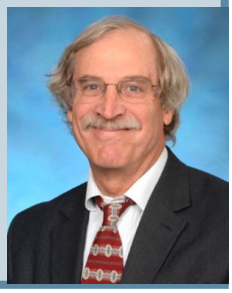
As ever, we hope that you and your family are happy and healthy. Now in its 24th year, the University of Maryland Amish Research Clinic continues to work out its mission to improve healthcare through research and to serve as a resource for health information and knowledge to the Amish Community.

We are proud of our Clinic staff, physicians, and researchers who work tirelessly at the ARC. Even more we are forever thankful for the unwavering support from the Amish Community and the many hours of donated time and effort of more than 7,000 Amish research volunteers! Our research now spans many diseases and health-related conditions such as diabetes, heart disease, cholesterol abnormalities, osteoporosis (weak bones), mental health and illness, and wellness and healthy aging to name a few. The Amish Community and the ARC Advisory Committee have helped us identify other disorders that are of concern to the community including Lyme disease, poison ivy, cancer, nutrition, and others that we have begun to address. But what are we most excited about? Our research has now entered a new phase. In collaboration with the Regeneron Genetics Center (where Dr. Shuldiner now works in addition to his continued work at the University of Maryland), we have gotten a lot of genetic (DNA sequence) information that has led to the identification of genetic variation in the community with important implications. Individuals who carry these genetic variants may be at higher risk for certain health conditions.

We are now in a phase of our work in which we offer research participants the opportunity to know about their genetic results so that steps can be taken to prevent or delay the health issue. This is important not only for research volunteers, but also their family members (For example, see pages 3 and 15 of this Newsletter describing our findings on a gene called *KCNQ1)*. Other gene variants we have found are of less certain medical importance and we are now working to better understand the consequences of these genetic variations (For example, see pages 3 and 4 describing new studies on genes called B4GALT1 and SERPINE1 as well as genotype-first studies of other genes). As our research proceeds, we expect many more discoveries that will have direct health impact in the Amish community as well as other populations around the world.

We hope you will continue to be engaged in the work we do together. Participating in research may provide health benefits including free medical evaluations and screenings for some common disorders and also 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; others 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. Please be sure to include your address so we can get back to you.

We hope you enjoy this issue of our Newsletter!



New Studies

KCNQ1 Cascade Screening Study

The KCNQ1 Cascade Screening Study is a follow-up to the KCNQ1 Return of Results study (see the inside of the back cover for details).

The *KCNQ1* gene change, which is present in about 1 in 40 Amish, causes Long QT Syndrome (LQTS). The study is open to individuals who participated in the original study and their first-degree family members (parents, siblings, and children). First-degree family members of someone with the gene change have a 50% chance of also having the gene change.

One goal of this study is to offer a simplified process for family members to be tested for the KCNQ1 gene change by offering free, in-home, saliva-based genetic testing (cascade screening).

Another goal is to assess the participants' opinions about receiving their genetic results and the cascade screening process for the *KCNQ1* gene change. This information is obtained by participants' completing questionnaires and possibly taking part in an in-person interview. Learning about participants' experiences will help us improve the way we present information to people who have genetic variants that need medical follow-up.

GAL-B4GALT1 & Serpine Call-back Study

Cholesterol (LDL) is a major risk factor for cardiovascular disease (CVD), the leading cause of death worldwide. LDL is governed by genetics and environmental factors, as well as the interplay between them.

We recently discovered a strong new association between a variant in the B4GALT1 gene and low LDL in the Old Order Amish. The variant has a frequency of 6% in the Amish while extremely rare in the general population.

The purpose of this study is to better understand how this variant works by comparing Amish individuals with and without the variant. The knowledge gained from this study may lead to the discovery of new medications for cholesterol.

This study has two parts. For both parts, gene variant carriers will be compared to non-carrier controls. Part A will involve questionnaires to obtain self-reported health data. Part B will involve a visit to the Amish Research Clinic for blood tests, an oral glucose tolerance test, EKG, echocardiogram, DXA, lung function tests, and some other blood vessel-related tests.

New Studies, continued

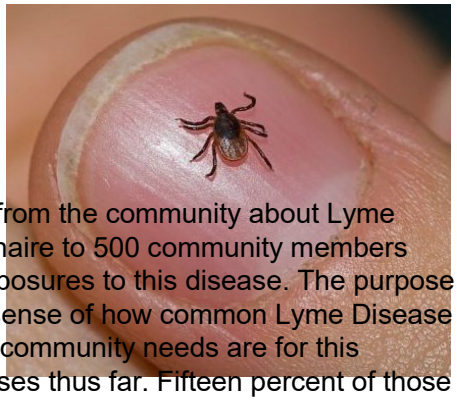
Poison Ivy Study

A skin reaction to poison ivy can be very uncomfortable to many of us who are exposed to this plant. The rash and itching characteristic of poison ivy is due to an allergic reaction to a resin called urushiol that is present on the leaves of the plant. It turns out that most, but not all, of the population is sensitive to urushiol.

Recent studies have suggested that sensitivity to the urushiol in poison ivy may be related to a person's genetics; that is, those people who are especially sensitive may have a genetic predisposition to having a stronger allergic reaction. We are starting a new study to test this idea.

There will be two parts to this study. In the first part, we will recruit a small number of people who we think may have a genetic variation that influences the allergic response and we will draw a sample of their blood to test in the laboratory. In the second part of the study we will perform actual skin testing in study subjects using very tiny controlled amounts of the oil. This may lead to a new therapy to prevent reactions to poison ivy by subduing this allergic response.

Lyme Disease



In response to concerns we have heard from the community about Lyme Disease, we have mailed out a questionnaire to 500 community members selected at random to ask about their exposures to this disease. The purpose of this questionnaire is a to get a better sense of how common Lyme Disease might be in the community and what the community needs are for this condition. We have received 190 responses thus far. Fifteen percent of those responding report that they have been diagnosed with Lyme Disease. We will report more results in the future.

Umbrella (or Genotype-First) Study

In our genetic analysis of over 6,000 Amish we have found some gene variants that clearly affect health. We have also identified a number of gene variants in which we need to get additional information to know whether they affect health. Some of the gene variations may affect a person's cholesterol level or risk of diabetes or kidney function.

For these variants, we are starting a new study that will include individuals with these variants and their relatives. We expect that the new information we collect will allow us to more confidently decide whether the new gene variants really do affect health, and if so, how to design our next step.

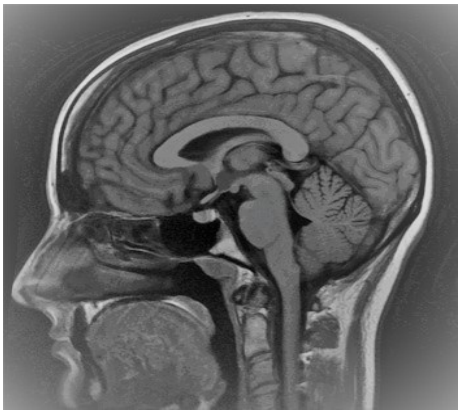
Ongoing Studies

Brain Body Connection Study

The purpose of this research is to find out more about brain differences that make it more likely an individual will have mental health problems by studying behavioral health and wellness.

We invite individuals with mental health problems and their family members to participate in the study.

Two full days are required to complete the testing and study participants are compensated for their time and effort. The first day takes place at the Amish Research Clinic and includes a clinical assessment and interviews. The second day takes place in Catonsville, MD and involves magnetic resonance imaging (MRI) of the brain. These images are used to understand the brain circuits, or wirings, which are related to mental health and often run in families.



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

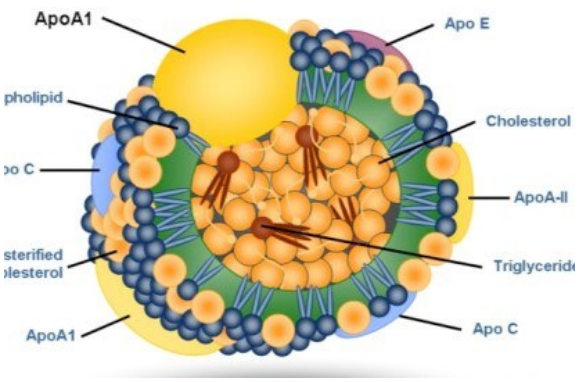
Ongoing Studies, continued

Amish Wellness Study

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.
We have found that high cholesterol and hypothyroidism (low thyroid function) are quite common in the Amish, and we are beginning to understand how genetic testing for certain conditions in Amish adults can help with heart health. 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, nearly 6,500 Amish individuals ages 18 and older have enrolled in the Wellness Study, which is funded by our partnership with the Regeneron Genetics Center LLC. Thank you!

Lipoprotein Turnover Study

Lipoproteins are special types of packages in the blood that help carry and deliver dietary fats and cholesterol to parts of our body that need them.



This study will help us learn more about people with genetic changes that affect how the body makes or uses lipoproteins. We will compare someone who has a genetic change with a sibling who does not have that change. Our study will look at the way these fat and cholesterol packages are made and broken down. This information might help in developing new ways to prevent or treat disorders of fat and cholesterol metabolism.

Sulfate Survey

Sulfate helps to regulate the function of many cells in our body. It helps the body make hormones; it modifies other nutrients and chemicals needed for brain function; and it affects how we break down and use medications. Regarding the effects of sulfate in the brain, there has been some speculation that sulfate deficiency could even be related to developmental problems in social behavior that affect the ways we socialize with other people.

However, little is known about how sulfate regulation in the human body may alter development or brain function. The Sulfate Study is a family-based research study that explores the impact of circulating sulfate levels on human communication, social interaction, and behavior. The study uses surveys and questionnaires to obtain information about how genes and other variables affect these factors. Two of the genes we want to study are related to the processing of sulfate in the body and can significantly change the levels of sulfate.

We are currently asking some of the participants in the Wellness study to complete the questionnaires. So far 311 people have agreed to participate. We have begun preliminary analyses on these and hope to complete the analysis in the coming months. The results obtained from this study may help us better identify factors that increase or decrease the risk of developing behavioral or social abnormalities, such as Autism Spectrum Disorder.

The Amish Family Diabetes Study (AFDS)

The goal of this project is to identify genes involved in the adult-onset form of diabetes, also called Type 2 diabetes. Identifying these genes may lead to new understandings of the disease and better ways to prevent or treat it. Over 1300 Amish have volunteered for the study and the search for diabetes risk genes is ongoing. One gene variation we identified that increases the risk for diabetes is called hormone sensitive lipase (HSL). We have also found that the Amish carry the same common gene variations as in the general population, each of which has a small effect on diabetes risk.

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. If you or someone in your family is experiencing these symptoms and would like to be tested. for diabetes, please call the clinic at 717-392-4948. All testing is free and usually done in your home.

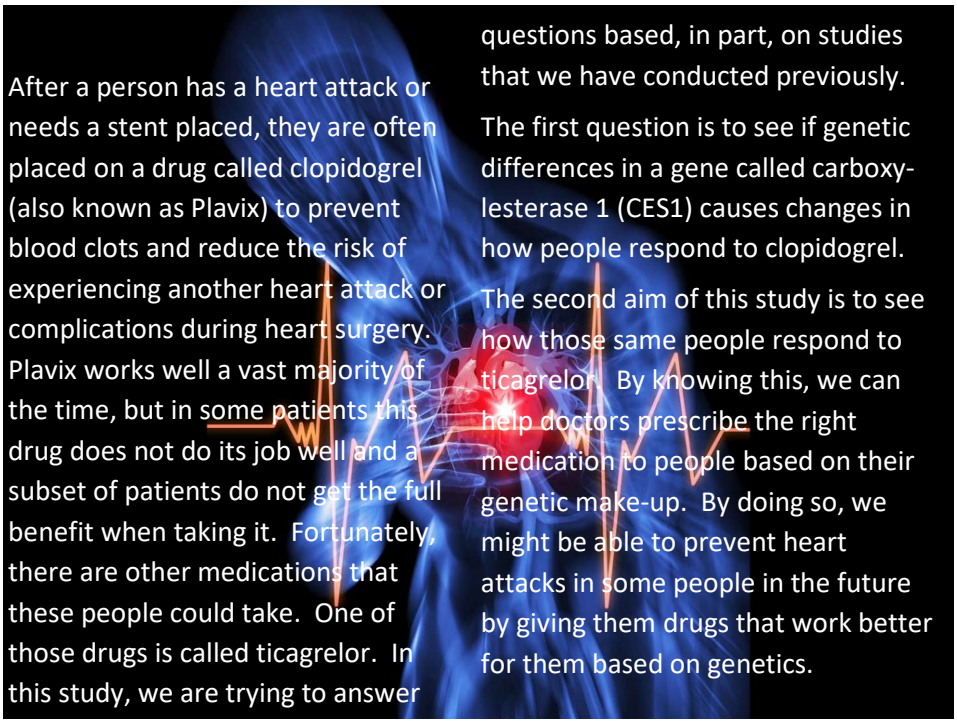
Ongoing Studies, continued

Until recently, medications have been made with the idea that each drug works pretty much the same in everybody. We now know that the "one size fits all" approach does not work for everybody. This can be due to differences in genes. We have studies that are looking at the effects of certain gene variations on medications that are currently being used to treat type 2 diabetes. The information from these studies may help doctors to choose the best medication or best dosage for each person.

Genetics of Response to Canagliflozin (GRC) Study

This study measures the effect of canagliflozin, an FDA approved drug that is used to treat type 2 diabetes, on healthy, non-diabetic people to see if a person's genes influence how well the canagliflozin removes sugar from the body. We also want to see if a person's genes influence whether they experience side effects from the drug. This study is open to those who have previously participated in an Amish Research Clinic Study.

CES1 Study



After a person has a heart attack or needs a stent placed, they are often placed on a drug called clopidogrel (also known as Plavix) to prevent blood clots and reduce the risk of experiencing another heart attack or complications during heart surgery. Plavix works well a vast majority of the time, but in some patients this drug does not do its job well and a subset of patients do not get the full benefit when taking it. Fortunately, there are other medications that these people could take. One of those drugs is called ticagrelor. In this study, we are trying to answer questions based, in part, on studies that we have conducted previously.

The first question is to see if genetic differences in a gene called carboxylesterase 1 (CES1) causes changes in how people respond to clopidogrel.

The second aim of this study is to see how those same people respond to ticagrelor. By knowing this, we can help doctors prescribe the right medication to people based on their genetic make-up. By doing so, we might be able to prevent heart attacks in some people in the future by giving them drugs that work better for them based on genetics.

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. In collaboration with many other groups around the world, we have found 60 genes that are important for bone health. Bone strength at “peak”, in the early 20s in women and mid 20s in men is 85% determined by genes. Bone loss, starting around age 50 is at least 30% due to genetic causes. This study remains open for recruitment and includes a free DXA bone density scan.

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 (15 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 many 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. Currently, this protocol is not active.

Perfect Pitch Study

Some of you may have heard about, or even participated in, the Perfect Pitch study. This study was inspired by one of our neurologist colleagues, who has an interest in how the brain works to process music. Some people have the rare ability to precisely recreate musical notes after hearing them only once. Moreover, ability to do this may run in families. In the Perfect Pitch study, we have tested participants to see if they have this trait with the goal of trying to map perfect pitch to particular genes to understand how the brain processes this type of information. We are currently not recruiting new research volunteers into this study.

Donation Message

The Amish Research Clinic is a nonprofit organization that has been a constant in our community. Freewill donations to help with operating expenses are appreciated. Checks can be made payable to the University of Maryland Baltimore Foundation/Amish Clinic (or UMBF/Amish Clinic), which administers gifts for the University of Maryland Amish Research Clinic. Kindly send your donation to:

University of Maryland School of Medicine
Office of Development
Attn: Traci Morgan
31 South Greene Street, Third Floor
Baltimore, MD 21201

Alternatively, you can donate online at: **medschool.umaryland.edu/Amishgift**

We want to thank those of you who have provided us support in the past. With your help, we have been able to purchase two new transport vans, provide free genetic confirmation of the KCNQ1 variant to participants, and cover other expenses associated with our clinic. If you have any questions, please call Pamela Lambert at 410.706.0419 or 717.512.6013.

Gifts to support the University of Maryland School of Medicine are administered by the University of Maryland Baltimore Foundation, Inc. A portion of any contribution to the University of Maryland School of Medicine may be used to enhance advancement efforts.

Studies in Analysis

Lp(a) Study

Cardiovascular disease (CVD) is a leading cause of premature deaths in the world. A high cholesterol level in the blood is an important risk factor for heart disease. Recent evidence from large groups suggest that a particular protein that is associated with cholesterol, called Lipoprotein (a) [Lp(a)], is an important determinant of heart disease and stroke. However, no practical method for lowering of Lp(a) levels with medicine is currently available. The objective of this study is to define how genes influence Lp(a).

We are particularly interested in two regions on chromosomes 6 & 11.

Participants of this study were asked to provide a blood sample and also undergo other tests to look at blood vessels in the neck and brain using ultrasound and MRI. Identification of the genes that influence Lp(a) levels may lead to the design of new treatment strategies to lower Lp(a) levels to prevent or treat heart disease.

[image is of cholesterol molecules]

Metabolic Impact of ApoC-III (MiACT)

Based on our exciting finding that about 1 in 20 Amish people carry a gene change that helps them to clear dietary fat from their blood faster and may help prevent heart disease, we are conducting 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 dietary fat, cholesterol and sugar, and how fat and cholesterol move around in their bloodstream. Over 100 people have enrolled in the study, which is funded by the National Institutes of Health. Some of these participants each recently graciously gave 16 hours of their time in one day for a special part of the study that allowed us to learn up close how having less apoC-III protects the heart.
The results were recently published in a scientific journal.

Seasonal Affective Disorder (SAD) Study

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. Our findings reporting the frequency of SAD and heritability of the disorder, both lower than expected, have been published in the Journal of Affective Disorders. We have also published an article in the Journal of Clinical Psychiatry on Australian twins and Old Order Amish, suggesting that in Australian twins but not Amish, seasonal affective disorder overlaps with bipolar disorder and schizophrenia. We finalized an article on a link between seasonality of mood and lower adiponectin, a hormone implicated in weight regulation, previously associated with depression, and a publication on measuring light in the Amish homes.

Zinc Study

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. We found that some people improve their insulin levels in response to zinc while others do not. This work was published in a major scientific journal.

Studies in Analysis, continued

Toxoplasma gondii Exposure Questionnaire

Toxoplasma gondii (T. gondii) is a microscopic organism found in about 10-20% of people in the US. In the Old Order Amish in Lancaster, we found it in approximately 50% of individuals. Most people with T. gondii are healthy but it can occasionally cause disease, mainly in people with a weakened immune system and babies born to women first exposed during pregnancy. Some research suggests that T. gondii may be associated with depression.

Questionnaires asking about factors that have been shown to contribute to being exposed to T. gondii were mailed in January 2016 to people who participated in the Wellness Study. Thank you to all who participated in this study.

The main result is that eating undercooked or raw meat, drinking unpasteurized milk and working with animals are each linked with being positive for T. gondii. We are also investigating links between different types of T. gondii and immune responses that may affect other organs, and genetic links with T. gondii exposure. We published an article on the heritability of neopterin, a marker of inflammation previously found elevated in T. gondii positivity. The heritability appeared to be small, and so neopterin levels in the blood might be more a reflection of a “state” under the influence of changes in the environment rather than stable traits. We have also found a weak association of T. gondii with mood states.

Chromosome 9 Study

Elevated low-density lipoprotein cholesterol (LDL) is a major risk factor for cardiovascular disease (CVD), the leading cause of death worldwide. LDL is governed by genetics and environmental factors, as well as the interplay between them. While environmental factors for LDL are very well established, most of the LDL genetic risk factors are still unknown. Identifying the genes related to LDL can help in better understanding the role of LDL in CVD leading to improved prediction, prevention and treatment of CVD.

We recently identified a variation in the B4GALT1 gene that is found in 6% of the Amish while extremely rare in the general population. It seems to be associated with lower levels of LDL. The overall goal of this project is to confirm this association and learn more about other effects of this variant. We are working to gain insights into LDL metabolism by researching carriers of this genetic variant.

Breast Density Study

Breast density refers to the amount of dense glandular tissue in the breast. It is measured by a routine mammogram or x-ray of the breast to detect unsuspected cancer. Dozens of studies over the past quarter of a century have suggested that dense breasts are more cancer prone. But no one knows exactly why. With the help of nearly 1,500 Amish women, we've been trying to answer that question by searching for the genes that affect density. We recently published an article, together with our colleagues in the U.S. and abroad, describing over half a dozen genes that influence breast density in the Amish and other populations of European descent. Several of these genes are also associated with the risk of breast cancer.

Pharmacogenetics of SGLT2 Inhibitors Study

This study, which began the summer of 2015, will help us have a better understanding of the effect of canagliflozin on healthy, non-diabetic people to see if a particular gene variation influences how well canagliflozin works in the kidneys to remove sugar from the body. People who participated in an Amish Research Clinic study before and carry certain gene variations participated in this study.

Pharmacogenetics of GLP1R Inhibitors Study

This study looks at how well exenatide and sitagliptin, FDA approved drugs that are used to treat type 2 diabetes, work in different people. We recruited healthy people that have participated in an Amish Research Clinic study before and carry a gene variation that may affect how well exenatide or sitagliptin lower blood sugar.

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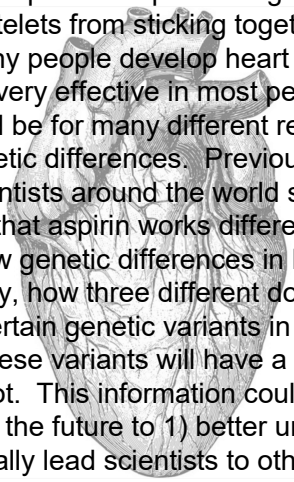
Studies in Analysis, continued

PEAR 1 Study



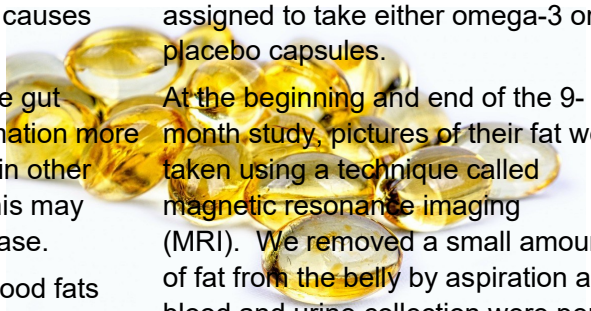
Aspirin is important in preventing cardiovascular disease by preventing cells called platelets from sticking together and causing blood clots, a main reason why people develop heart attacks. In combination with other drugs, aspirin is very effective in most people but in some it does not work well. This could be for many different reasons, one of which is that some people carry genetic differences. Previous studies conducted at the ARC and by other scientists around the world suggest that a gene called PEAR1 may be a reason that aspirin works differently in some people. In this study we tested how genetic differences in PEAR1 influence response to aspirin - specifically, how three different doses of aspirin work in people with and without certain genetic variants in PEAR1. We expect that people who contain these variants will have a different response to aspirin than those who do not. This information could be very important to researchers and doctors in the future to 1) better understand how aspirin works in people, 2) potentially lead scientists to other drug targets that could prevent heart attacks, and 3) aid doctors to prescribe the right dose of aspirin based on the patient's genetic make up to prevent or treat a heart attack.

Omega 3 / Fish Oil Study

This study is designed to learn whether omega-3 fish oil can help to reduce the type of fat that causes health problems.

Fat that accumulates in the gut seems to promote inflammation more than fat that accumulates in other areas of our bodies and this may increase risk of heart disease.

Omega-3 fish oil lowers blood fats (triglycerides) but we are not sure whether it also reduces inflammation of fat. To be eligible for this study, Amish men and women older than 18 years needed to have a fasting triglyceride levels above 150 with an increased waistline. Participants were assigned to take either omega-3 or placebo capsules.



At the beginning and end of the 9-month study, pictures of their fat were taken using a technique called magnetic resonance imaging (MRI). We removed a small amount of fat from the belly by aspiration and blood and urine collection were performed at the beginning and end of the study. We are analyzing the data currently.

Return of Genetic Results

KCNQ1 Return of Results

Through our genetic analyses, we identified a variation (change) in the gene *KCNQ1* that causes Long QT Syndrome (LQTS). The "QT" interval is a measurement from an electro-cardiogram that tells us about the electrical activity of the heart.

LQTS is a disorder of that electrical activity that increases the risk of fainting and sudden death throughout the lifespan, although 50% of people never have symptoms. LQTS causes at least 10% of crib deaths and can cause sudden death in children and adults, most commonly during physical activity. Changes in *KCNQ1* are present in about 1/2000 in the general population but are present in 1/44 in the Amish. Medications called beta blockers are very effective in treating LQTS, preventing fainting and sudden death by 70-90%. Beta blockers are generally safe and do not cause side effects in 95% of people who take them.

In this study, we gathered information from 88 people with the gene change in *KCNQ1.* We found that people with the *KCNQ1* variant had a longer QT than people who do not have the variant, were more likely to have fainted (33% compared 20%) and to have a close family member who died before age 30 (5% in carriers vs 0 in non-carriers). We gave this information to people who participated in the study and gave recommendations to take a beta blocker (through their local doctor) for those who met the criteria for treatment. Of people with the *KCNQ1* variant, half of their children are expected to have the same variant, so we recommended that they be tested. Genetic testing is available through the Clinic for Special Children.

Amish Research Clinic Team:

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Studies from the Amish Research Program have been described in over 316 publications. These can be viewed on this website:

https://www.ncbi.nlm.nih.gov/myncbi/collections/47782571/

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Our Mission

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.