



Multiple Autoimmune Disease Genetics Consortium

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www.madgc.org

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THE MADGC STUDY: THE PRINCIPAL INVESTIGATOR MAKES HIS FINAL REPORT AND LOOKS FORWARD

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Since we last contacted you, there have been more exciting developments in the MADGC study.

Last year, we discovered a new gene that confers a two-fold risk for several autoimmune diseases, including rheumatoid arthritis, lupus, juvenile diabetes, and both major types of autoimmune thyroid disease. This really is the first major gene that clearly carries overlapping risk for different forms of autoimmune disease. This is an exciting discovery for us, because the goal of finding and understanding these types of genes is exactly the reason that the MADGC study was begun over five years ago. You can find a copy of this just published work online at www.madgc.org.

REGULATING THE IMMUNE SYSTEM

So, what do we actually know about this gene? It is called PTPN22 — admittedly, not a very interesting or informative name. But PTPN22 does important things for regulating the immune system. Among other things, it appears to set a threshold — a kind of trigger point — for turning the immune system on and off. We know that this gene is active in T cells — the so-called quarterback cells of the immune system. We also know it is clearly active in several other types of cells involved in immune defense and inflammation. Until recently, scientists were not paying much attention to this gene, so there is still a lot that we do not know about how it works. However, with the discovery that PTPN22 is involved in multiple autoimmune diseases, there has been a tremendous increase in work on this gene in the scientific community. MADGC investigators are in the forefront of this effort.

The genetic variant of PTPN22 that we found is present in about 15% of the normal population, most of whom do not have autoimmunity. This gene is a normal gene and probably confers some advantages — for example, perhaps a slightly better ability to defend against viral infection. This illustrates the fact that certain combinations of normal genes, along with environmental factors, ultimately explain why certain individuals get autoimmune diseases. But this is just the beginning of an exciting new effort to discover all of these genetic variants.

We have now enrolled over 360 families in the MADGC study; it is one of the largest collections of such families in the world and is proving to be an invaluable resource for researchers across the country. Looking forward, we may ask you to provide us with follow up information and another blood sample. We also are particularly interested in obtaining

additional information and blood samples from some of your relatives who are not affected with autoimmune diseases. Kindly encourage your family members to participate.

THANK YOU

The five-year Multiple Autoimmune Disease Consortium (MADGC) study is coming to a close and this will be the final newsletter. All of us here want to thank you for everything that you have done to help make the MADGC study a success.

A FOLLOW-UP STUDY

We are now in the planning stage of a follow-up study, which we have named, not surprisingly, MADGC 2. This new study will have slightly different enrollment criteria; there will be an emphasis on the disease-free siblings of people with autoimmune diseases. In this study we will explore the factors that explain why these siblings are protected from getting clinical autoimmune disease, and also attempt to identify factors that can predict the future development of autoimmune disease. If we can do that, we may be able to intervene early to prevent the disease before it even starts.

Thanks to new technologies that are being developed to understand the genetics and biology of autoimmunity, this is an exciting time to be involved in medical research. But this study is really about people. Without the kind assistance of public-spirited individuals like you, it would not have been possible to conduct our study.

Thank you for participating in the MADGC study.



THE ROLE THAT ANTIBODIES PLAY

Any attempt to understand the causes of autoimmune disease must include a discussion of antibodies and the role that they play.

Antibodies are Y shaped proteins produced by a special kind of white blood cell called a B lymphocyte. Normally present in the bloodstream, antibodies are essential for our immune protection.

Using the two short ends of the Y as a precise germ identification device, an antibody can activate the immune system to act against a specific target or antigen. Our body is stimulated to produce antibodies when infected, or vaccinated against, a particular antigen.

Antibodies help destroy their target both by turning on destructive proteins in the blood and by stimulating white blood cells to attack. People born without the capacity to produce antibodies cannot control common infections and are very vulnerable to diseases such as severe pneumonia. Replacement of antibodies, given as an IV infusion, can return immune function to virtually normal in these cases.

TURNING AGAINST THE BODY

However, this precise identification system can turn against the body and cause a targeted immune attack of vital organs. This is the case in many autoimmune diseases such as Hashimoto's, Graves, diabetes, and lupus. In these illnesses, the body makes specific antibodies to a part of itself, such as the thyroid gland, and causes its destruction. We know that these antibodies may be present well before the patient becomes sick. In other cases, the antibodies can be measured in the blood without development of an illness. Some diseases, such as rheumatoid arthritis, have high amounts of autoantibodies whose precise role is still unclear.

Researchers are currently trying to understand what causes the breakdown in the careful immune balance that results in production of autoantibodies. In addition,

research is being done to understand why some people are protected against development of a disease, in spite of the presence of antibodies. By better understanding the link between antibody production and autoimmune disease, we hope to be able to prevent the development of these illnesses. Our goal is to identify what causes the breakdown in communication, which allows a valuable friend to become a foe.

A PERSONAL NOTE

The five-year enrollment period for the MADGC study has come to an end. The information and blood samples that you and your family have so generously provided are still being analyzed. All of the data that we have collected during these past five years will be stored in accordance with strict federal government guidelines to ensure confidentiality.

Last summer, we re-contacted families with six or more members who were affected by autoimmune disease. We asked unaffected members of these families to provide us with blood samples. This was an ambitious undertaking and we were amazed by the commitment shown by those of you who participated. It was because of you that this effort was a success.

During the past five years we have been invited to your family reunions, picnics and birthday parties to collect your blood samples. You have told us many stories about your families that have been an inspiration to our research team.

As we move into our follow-up study — called MADGC 2 — we very much hope that we will have the opportunity to contact you again. In the meantime, you may want to follow our progress by logging on to our website: www.madgc.org

The entire study coordinator team is thankful for the important contribution that you have made to the MADGC study.

With best regards,
North Shore University Hospital: Bonnie Gonzales, Marlana Kern, Gila Klein, Mary McFeely & Loreta Palazzo; University of California-San Francisco: Molly Mollin, Sarah Kupfer & Jennifer Pearce; University of Minnesota-Minneapolis: Jill Novitzke, Karina DiLuzio, Jen Islam & Laura Broderick



A PRECIOUS GIFT

The blood sample that you so generously provided is a precious gift to the research community.

Blood is a rich source of information that is used by researchers to obtain a better understanding of autoimmune disease. Genes and proteins found in the blood cells of patients with autoimmune diseases are altered when compared to individuals who do not have an autoimmune disease. Analyzing the pattern of these alterations leads to the discovery of new biomarkers. These biomarkers can enhance our understanding of the disease process, which can result in better diagnosis and treatment of patients.

What happens to your blood sample when it arrives at the laboratory? The research coordinator first de-identifies the sample by removing any personal information. The sample is then given a random number prior to being processed in the laboratory. The blood is then processed to separate different blood components such as white blood cells, genetic material (DNA and RNA) and plasma, which is the liquid part of blood and serum. All of these blood components can provide clues as to the changes that occur in a patient as a result of the disease process.

Recently, scientists made a breakthrough by sequencing the human genome. A genome contains all of an individual's DNA, including your 23 pairs of chromosomes and the genes on them. Genes contain information to make proteins that determine everything from why we look the way we do to our ability to fight infection. DNA is made up of four chemicals called bases abbreviated as A, C, G and T. The human genome has 3 billion pairs of bases.

Researchers are currently benefiting from a technological revolution wherein large-scale analysis of DNA, genes and proteins can be processed in a relatively short period of time. We now can use a DNA chip, which is, in prin-

cipal, similar to a computer chip. Using a DNA chip enables researchers to obtain information for all the variation in DNA, genes and protein in just a matter of days. Analysis of the data gathered from such experiments requires the use of large computer databases. The end result of such complex analyses is a better understanding of the autoimmune disease process.

We are applying these new technologies to the gift of your blood sample. Our goal is to translate our research findings into improved diagnosis and treatment of people with autoimmune disease. But this would not be possible without your precious gift.

WANT TO LEARN MORE?

If you would like to learn more, visit "DNA From the Beginning" at www.dnafb.org. This excellent and informative site, which calls itself an "animated primer on the basics of DNA, genes and heredity", is run by the Cold Spring Harbor Laboratory, a research and educational institution located on Long Island, New York.

UPDATING YOUR RECORDS

Keeping your records up-to-date is important to us, so we ask that you kindly fill out the attached questionnaire and send it back to us. Please understand that you are under no obligation to answer any of these questions and that any

answers you do provide will be kept strictly confidential in accordance with federal government regulations.

**SCIENTISTS
AND RESEARCHERS
CANNOT DO IT ALONE...
WE NEED YOUR HELP!**

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