

INSTITUTE: National Institute of Environmental Health Sciences

STUDY NUMBER: 03-E-0099 PRINCIPAL INVESTIGATOR: Frederick Miller, M.D., Ph.D.

STUDY TITLE: Pathogenic Studies in Families with Twins or Siblings Discordant for Systemic Rheumatic Disorders

Continuing Review Approved by the IRB on 11/29/10

Amendment Approved by the IRB on 11/29/10 (N)

Date Posted to the Web: 1/25/11

Adult Proband or Twin-Sibling of Proband Evaluated at NIH

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

THE PURPOSE OF THIS STUDY

Researchers at the National Institute of Environmental Health Sciences (NIEHS), in collaboration with the Centers for Disease Control (CDC) and other researchers are conducting a study to try to understand why some persons develop certain diseases while other persons do not. Scientists believe that differences in peoples' responses to certain exposures in the environment, as a result of differences in the genetic makeup of the person, may determine who develops certain diseases.

You are being asked to enroll in this study because you or one of your brothers or sisters has a form of disease, which involves abnormalities in the immune system called rheumatoid arthritis (RA), systemic lupus erythematosus (lupus), systemic sclerosis (scleroderma) or polymyositis, dermatomyositis or inclusion body myositis (myositis). These diseases together are called systemic rheumatic diseases.

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This study is being conducted in families in which two siblings of the same gender (either two brothers or two sisters) are within four years of age and one has developed a systemic rheumatic disease and one has not. The purpose of the study is to see if there are differences in the blood cell metabolism, the types of cells in the blood, the exposures, or the genetics of the brothers or sisters, which might explain why one has developed disease and one has not. Your parents, and in some cases your children, will also be asked to enroll in this study. About 400 pairs of brothers or sisters and 100 normal controls will be enrolled in this study.

RESEARCH TESTS OR PROCEDURES FOR THIS STUDY

If you agree to participate in this study, doctors involved in this protocol will see you at the NIH Clinical Center where you will have a thorough medical evaluation. This evaluation will involve obtaining your medical records, answering questions about your medical history, completing written questionnaires, undergoing a physical examination and donating blood, urine and possibly other clinical specimens for research purposes.

We will ask you to do the following in this study:

- 1) Allow us to obtain and review your past medical records from your doctors or other health care providers. The information from your records will be kept strictly confidential.
- 2) You will spend about 2-3 hours completing forms about your past medical history and the types of exposures you have had at work, at home and elsewhere. If you have a systemic rheumatic disease, you will also be asked if you have had certain infections, received vaccinations, were taking certain medications or dietary supplements, had certain types of sun exposure, used tobacco, or experienced stressful events in your life during the year before the diagnosis of your disease. If you are a brother or sister of a person who has a systemic rheumatic disease, you will be asked the same questions covering the same period of time.
- 3) You will undergo a careful medical history and physical examination by your physician at the NIH who will also complete forms describing the findings from this evaluation. This evaluation is performed to document the features of your systemic rheumatic disease or to confirm that you do not have these illnesses. If any abnormalities or diseases are detected that your health care provider did not previously identify, additional testing may be performed or recommended for clinical care purposes only.
- 4) You will have about 6 tablespoons (75 milliliters) of blood and a first morning urine collected for a number of clinical and research tests. Blood drawing involves cleaning the skin of the arm with alcohol. A needle is then inserted into the vein. Blood is then quickly withdrawn using a special tube or syringe. Urine collection involves urinating into a clean cup with a lid.

The following tests will be performed on the blood and urine samples:

- a) To confirm that you do not have certain diseases or medical problems that you are unaware of, a blood specimen will be collected for routine clinical chemistry and other blood studies, including tests for antibodies found in patients with rheumatic diseases.
- b) Because certain environmental exposures may cause certain diseases, we will be testing your blood and urine for evidence of past toxic exposures and if you have had or have certain infections. The NIH laboratories will perform some of these tests. However, our collaborators, including the CDC, will perform some of these tests in their laboratories.

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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- c) The hereditary factors that determine many of our physical characteristics and may predispose to disease are called genes. To identify which genes may be related to disease, DNA, the chemical substance that contains the genes, is extracted from blood or tissues from healthy persons and from those with disease and compared using statistical methods. We will be testing your blood for the genes for human leukocyte antigens (HLA) and tumor necrosis factor (TNF). This will allow us to determine if certain forms of these genes are more common in patients with systemic rheumatic diseases compared to unaffected brothers or sisters and compared to normal volunteers.
- d) If you are a twin, we will be comparing the metabolism in your blood cells with the metabolism in your twin's blood cells to see if persons with systemic rheumatic diseases have a different metabolism. The metabolism in your blood cells is controlled by how some genes are activated (turned on) and some are deactivated (turned off). Because this pattern of gene activation may help us understand how diseases occur, research tests on blood or urine samples will determine the types of genes and proteins that are active in your blood cells.
- e) Recent studies suggest that during pregnancy or delivery, cells from the mother and baby may be exchanged, may circulate in the body for many years, and possibly may cause problems. For this reason, research tests will be done to see if there are cells from your mother or, if you have had children, from your children circulating in your blood. Also, if you are found to have cells in your blood with genetic markers suggesting that they are from other persons, and you have had children, we will ask you to explain this study to your children so they can consider enrolling so we can test their blood to determine if their cells are in your blood.
- f) We are asking you to let us have samples of your blood and urine to store for future research on the causes of rheumatic diseases and their complications. We will also ask to collect any past blood or tissue biopsy specimens that are no longer needed for your clinical care, for research purposes. Your blood and urine samples with your name on them will be processed in the NIH and by our contractors for testing and for storage in a freezer. We will store all your samples with a code and not with your name. Coding is done to protect your identity and only those researchers closely involved with the progress of the study will have access to the locked files that can link the code to your name or other private information. These coded samples will be used to complete studies described in this consent form by investigators involved in this protocol.
- g) As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

As described above in item 4 c), we are performing genetic tests for research purposes to define possible genetic risk factors for myositis. A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. According to this law, health insurance companies or group health plans (as of May 21, 2010) cannot request your genetic information or use it to make decisions about your eligibility or premiums; and employers cannot use it in deciding to hire, promote, or fire you or in setting the terms of your employment (as of Nov 21, 2009). Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. The following link contains details about this law: <http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf>. You may ask your research team for additional information or a copy of The Genetic Information Nondiscrimination Act of 2008 informational document.

In addition we will ask you to contact your parents to explain this study so they can consider enrolling. If other members of your family were interested in participating, they could either call our toll-free telephone number (1-888-271-3207), or

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relay their verbal permission for us to call them. In either case, your relative would be given an opportunity to discuss this study with us before deciding whether they might wish to participate.

We will report laboratory and other results that may have an important effect on your health to you and your doctor. The investigators conducting this study do not plan to provide you with the results of any of the research tests mentioned above because further research may be necessary before the results are meaningful. If meaningful information is developed from this study that may become important for your health, you and your health care provider will be informed when it becomes available. By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Frederick Miller.

You may be contacted in the future for additional information or to give additional blood or urine samples, and you may be asked to consider participating in future studies. Your participation in this and all future studies is completely voluntary. You may withdraw from this study at any time, and you may decline to participate in any follow-up studies, without in any way affecting your eligibility for participation in future research at the NIH.

QUESTIONNAIRES AND FOLLOW-UP EVALUATIONS

In order to determine if you have had certain exposures in the past, we will ask about your past occupations, hobbies, other activities, drugs and dietary supplements, vaccinations, infections and stressful life events, by having you complete questionnaires. Depending on the answers to these questions, you may be contacted by phone by persons involved in this study to clarify certain answers and to obtain more detailed information about your occupations. We will also ask you to fill out several questionnaires to assess your ability to function and how active your systemic rheumatic disease is at this time. All this information will be kept strictly confidential.

If your medical condition changes in an important way, we ask that you contact your health care provider or your NIH doctor to discuss these changes and determine if you should be evaluated. If you are the unaffected sibling or twin of a subject with a known rheumatic disease and a doctor tells you that you have developed a new autoimmune or rheumatic disease, we ask that you contact your NIH doctor to discuss these changes and determine if you should be evaluated. You are free to call your NIH doctor at any time to discuss your medical condition or any aspects of the study. If you develop a new rheumatic or autoimmune disease please contact your NIH physician.

RISKS OR DISCOMFORTS TO YOU IF YOU TAKE PART IN THIS STUDY

You may reasonably expect to experience the following risks and/or discomforts. The major risks of blood drawing involve the pain of the needle puncturing the skin and the risk of getting a bruise. There is also a small chance of infection or bleeding around the spot where the blood was drawn and a very few persons may faint during blood drawing. You will receive appropriate treatment for any complications of this sort.

Some people are concerned that research about genetic causes of illness may give information that is not only about themselves, but also about their relatives and other groups of people who are like them. Because the diseases we are studying result from many genes and exposures, it is unlikely, although possible that we will learn genetic information in this study that can be used to diagnose or predict rheumatic diseases in you or your family.

Issues of adoption and paternity (biological fatherhood) may be discovered in the course of this study. It is our policy not to discuss such information with you unless it has direct medical implications for you or your family.

The researchers will learn new information about your cells and your DNA, but since none of the changes being looked for is known to cause any disease, there is very little risk that this information could be damaging to you in any way.

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However, it is possible that the researchers will learn new information that may link the changes seen in participants' blood samples to a specific condition or disease and this could affect your ability to obtain health insurance in the future. NIH and the Clinical Center, like other hospitals, may be required to release such information to insurance companies if you have signed a release of information form.

BENEFITS TO YOU OF TAKING PART IN THIS STUDY

This is a research study. By donating your blood, urine and biopsy samples you may not personally benefit from this study, but you may be helping scientists discover genetic differences in our cells that make some people more sensitive to environmental factors or in understanding which environmental exposures may be related to disease. The physicians involved in your care at NIH will not take over your clinical care. We will, however, work with your referring physician and make treatment recommendations to your doctor if needed. You may potentially benefit directly from participation in this study by undergoing a very thorough clinical evaluation, the results of which will be shared with your doctor in order to help them plan the most appropriate treatments for you. If we discover any new information during the study that might affect your health, we will notify you and your health care provider immediately.

WHAT OTHER CHOICES YOU HAVE BESIDES TAKING PART IN THIS STUDY

You have the alternative of not participating in this study.

WHAT WILL HAPPEN TO THE SAMPLES OR INFORMATION THAT ARE COLLECTED FROM THIS STUDY

Your DNA/blood/cell/urine/other samples/study records will remain stored indefinitely in order to allow for the studies to be completed and to allow for retesting of your samples as necessary. Your DNA/blood/cell/urine/and other samples will be stored at two sites: the National Institutes of Health and the repository of the National Institute of Environmental Health Sciences. The reason for duplication of long-term storage is to insure against accidental loss of frozen samples. All stored DNA/blood/cell/urine samples and information generated from this study will be identified by a code and not your name. This code will be kept secure in a locked area or in computer files that only Dr. Miller and a few specific investigators or their designees in this study can access with a password.

Your coded information or samples may be sent to other investigators involved in this protocol for research purposes, as defined in this protocol. These investigators will not know your name and will not know which samples are yours. These collaborating investigators are located at: the Spanish National Cancer Center in Madrid Spain; the Center for Biologics Evaluation and Research, FDA in Bethesda, MD; the Centers for Disease Control and Prevention in Atlanta, GA; the Medical University of South Carolina in Charleston, SC; the Dermatology Institute in Rome Italy; Duke University School of Medicine in Durham, NC; the University of California in San Diego, CA; the Oklahoma Medical Research Foundation in Oklahoma City, OK; IWK Health Centre, Halifax, Canada Uppsala university, Uppsala, Sweden, Baylor Institute for Immunology, Dallas, TX , The National Institute of Environmental Health Sciences, Research Triangle Park, NC and Arizona State University in Tempe, AZ.

Your samples will not be available for routine care or commercial diagnostic testing. It is possible that your samples or study records may be shared anonymously with other investigators for other research use beyond the scope of this study. Such usage will be strictly anonymous, in that no identifying information about you, including your name, will be provided to the researcher, and there will be no way for the researchers to link these samples back to you.

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WHAT TO DO IF YOU DECIDE TO WITHDRAW FROM THIS STUDY

You may withdraw from this study at any time by providing notification to your primary NIH doctor. You may ask to no longer be contacted by us and to not return to the NIH. In this case, we will no longer contact you by phone or mail you any further questionnaires. If you decide to withdraw from this study, it will not in any way affect your eligibility for medical care or participation in future research at the NIH.

COMPENSATION

You and your referring health care provider will each be monetarily compensated \$100, for the time and inconvenience involved in participation, upon your initial enrollment into the study. At the end of the study you and your referring health care provider will also be compensated \$100 at your final visit. In some cases, you may be asked to return for one or more additional visits to repeat some of the research tests, and if this occurs, you and your local health care provider will again each be monetarily compensated by a payment of \$100 for each visit

CONFLICT OF INTEREST STATEMENT

1. The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process <http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf>. You may ask your research team for additional information or a copy of the Protocol Review Guide.

2. This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

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COMPLETE APPROPRIATE ITEM(S) BELOW:

CONSENT TO STORE YOUR SAMPLES FROZEN FOR POSSIBLE FUTURE RESEARCH

A. Adult Patient's Consent

Thank you for agreeing to participate in this study. Now we would like your permission for the NIH and its research partners, including the CDC, to store the remainder of your blood, urine and other samples for possible future research. Your frozen samples will be stored under a number code. Only the NIH study researchers will be able to match this code with your name. The remainder of your coded specimens may be used for additional studies of systemic rheumatic diseases and their causes. Your remaining coded samples may also be used to study disorders unrelated to the diseases being studied in this research. The researchers will not have access to your name or any identifying information about you.

Your consent to frozen storage of your samples does not affect your ability to participate in this study. If the results of these future tests are medically significant, we will attempt to report them to your health care provider.

- I AGREE to frozen storage for possible future research**
- I DO NOT agree to this**

Signature of Adult Patient/Legal Representative Date

Signature of Witness Date

B. Parent's Permission for Minor Patient

Thank you for agreeing to have your child participate in this study. Now we would like your permission for the NIH and its research partners, including the CDC, to store the remainder of you child's blood, urine and other samples for possible future research. The frozen samples will be stored under a number code. Only the NIH study researchers will be able to match this code with your child's name.

The remainder of the coded specimens may be used for additional studies of systemic rheumatic diseases and their causes. Your remaining coded samples may also be used to study disorders unrelated to the diseases being studied in this research. The researchers will not have access to your child's name or any other identifying information.

Your consent to frozen storage of your samples does not affect your child's ability to participate in this study. If the results of these future tests are medically significant, we will attempt to report them to your child's health care provider.

- I AGREE to frozen storage for possible future research**
- I DO NOT agree to this**

Signature of Parent(s)/Guardian Date

Signature of Witness Date

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to frozen storage of study samples.

Signature of Parent(s)/Guardian Date

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE
FROM NOVEMBER 29, 2010 THROUGH NOVEMBER 28, 2011.**

Signature of Investigator Date

Signature of Witness Date

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Frederick W. Miller; NIH Building 10, Room 4-2330, Telephone: 301-451-6280 or toll free at 888-271-3207. Other researchers you may call are: Dr. Lisa Rider, Anna Jansen or Dr. Irene Whitt at the same telephone numbers. You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative

Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian

Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian

Date

Print Name

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE
FROM NOVEMBER 29, 2010 THROUGH NOVEMBER 28, 2011.**

Signature of Investigator

Date

Signature of Witness

Date

Print Name

Print Name

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)

• Adult Patient or • Parent, for Minor Patient

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File in Section 4: Protocol Consent