CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

MEDICAL RECORD

• Adult Patient or • Parent, for Minor Patient

INSTITUTE: National Human Genome Research Institute

STUDY NUMBER: 01-HG-0109

PRINCIPAL INVESTIGATOR: William A. Gahl, M.D., Ph.D.

ADJUNCT PRINCIPAL INVESTIGATOR: Ann C.M. Smith, M.A., CGC

STUDY TITLE: Natural History Study of the Clinical and Molecular Manifestations of Smith-Magenis Syndrome (SMS)

Continuing Review Approved by the IRB on 06/30/15
Amendment Approved by the IRB on 04/07/15 (G) Date Posted to Web: 07/02/15
Child with SMS - Offsite Participation

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.

WHY IS THIS STUDY BEING DONE?

You and your child are being asked to participate in this study because your child is known or suspected to have Smith-Magenis syndrome (SMS), a rare neurobehavioral syndrome usually caused by a deletion of chromosome 17p11.2; in less 10% of cases it is due to a mutation in the RAI1 gene. There are several ways you/your child may participate in this study that do not require you/your child to travel to the National Institutes of Health (NIH). The attached Information Sheet on Smith-Magenis Syndrome (SMS) explains the study and aspects of our research that can be done in the home setting with consent for “offsite enrollment”. Please read the sheet carefully, and ask questions about anything that you do not understand. We want you to understand the study before signing the consent form. At the discretion of the Adjunct Principal Investigator, we may ask to schedule your child to be seen for a comprehensive evaluation at the National Institutes of Health that may last several days (2-5). This will require a separate consent.
The main goals of the study are:
- To understand the medical, behavioral, and learning problems in people with SMS.
- To learn more about the region of chromosome 17p11.2 gene or genes that cause SMS.
- To learn if specific genetic changes in the SMS region on chromosome 17 results in specific medical problems.
- To identify features that must be present to make the diagnosis of SMS.
- To learn about the impact on families of having a child with SMS.

**WHAT IS INVOLVED IN THE STUDY?**

*Telephone Eligibility Screen:* Interested participants/families will be contacted by the Adjunct PI (Ann C.M. Smith), or a member of the NIH SMS Research Team, to obtain screening information, explain the details of the study, and answer questions. We will ask your consent to permit us to collect your child’s past medical records and genetic test results for review. You will be sent consent forms and study questionnaires (SMS RESEARCH PACKET) to complete and return to us.

*SMS Medical Record Archive:* Submission of copies of your child’s medical, genetic, growth and developmental records for review by the Adjunct-PI (Ann Smith) and SMS Research Team. This should also include documentation from the physician/geneticist who confirmed your child’s diagnosis and/or copies of past laboratory testing. We may also ask to request that copies of your child’s past MRI/CT scans and/or X-ray films be sent to NIH for review. We may ask you to send us pictures of your child (digital or scanned) in infancy and current age to keep on file.

*SMS Research Packet:* You will have the option of completing the SMS RESEARCH PACKET either in hardcopy format or using the secure web-based NIH Clinical Trials Survey System (CTSS) with a password we provide to you. This usually takes about 1.5-2 hours to complete in a single or multiple shorter time sessions. Periodically, participants (or their parents) will receive new questionnaires to keep information updated and to investigate new topics of interest.

*SMS Home Assessment of Sleep (SMS-Has):* Using non-invasive measures that are part of the SMS-HAS, we hope to learn more about the sleep disturbance in SMS and its relationship to mood and behavior. This aspect of the study is conducted in the home setting. To document the disrupted sleep-wake cycle and hyperactivity that accompanies SMS, your child will be asked to wear a wrist activity monitor (Actiwatch) for an extended period of ~2-5 weeks or longer as tolerated (up to 6 months). You may be asked to complete a sleep history questionnaire and daily sleep diary of your child’s sleep pattern and indicate their behavior/mood for the day. We may ask you to take serial measurements of your child’s body temperature (8 times/24 hours) for several days using a digital thermometer that we provide. To measure melatonin and other biochemical markers, we may ask to collect single or serial samples of saliva (spit) and/or urine at home, using a collection kit we provide.

*Molecular Genetic Studies of Smith-Magenis Syndrome (SMS)*

As part of this study we will be collecting and storing biological specimens on your child and parents for ongoing and future research to study the SMS deletion and gene(s) of interest. A blood collection kit with instructions will be sent to you to have your/your child’s blood drawn and sent back to NIH, at NIH expense. About 2-3 teaspoons of blood will be drawn from adults and 1-3 teaspoons from children (depending on their size) by standard procedures. NIH will cover the costs of blood drawing and return shipment.

Arrangements to collect a tissue sample during elective/scheduled surgery can also be made. Prior arrangements are needed to optimize collection of fresh tissue samples, which require special handling. The tissue(s) will be cultured and stored and permanent cell lines created for use in future research projects related to SMS. In cases where pathological tissue blocks are available, we may ask your permission to have these sent to us.
Biological specimens obtained for research purposes will be stored in a freezer in our laboratories during the study. Genetic analysis through DNA testing will be performed to further understand the molecular genetic basis for your child's diagnosis; this may involve sequencing of your/your child's entire DNA to look for changes. (See next section.) A cell line may be developed from the blood and/or tissue sample(s) your child initially provides to allow us to study your child's DNA/RNA in the future without having to take another sample. This lets us do more research on SMS when new techniques become available or as new genes within the SMS deletion region are identified. The samples will be studied for research questions having to do with SMS by researchers associated with this research project. If necessary or helpful, DNA/RNA, tissue or fluid specimens from you/your child may be sent to experts at other centers for analysis. If a research finding has important health implications for your child, every effort will be made to have it confirmed by an approved clinical diagnostic laboratory, so we can share the test result with you. If there are any risks to you or your family associated with these scientific studies that are not covered in this consent form, your consent will be obtained before such studies are performed.

By agreeing to participate in this study, you do not lose any rights that you may have regarding access to and disclosure of your child’s records.

**PROVIDING YOU WITH YOUR GENETIC INFORMATION**

We plan to use advanced DNA techniques to test for changes in genes that may contribute to your child’s known or suspected SMS diagnosis. The new DNA sequencing technology looks at all the human genes we know about; this is known as **genome sequencing**. We are looking to see if any of these genes have changes that cause or contribute to SMS. This research may take years. Because this new technology is much more detailed than previous DNA testing, we would like to explain what we plan to do and get your permission to do this.

1. Genome sequencing and other forms of genetic testing are research tests that can provide various types of results. For example, we can find gene variants that are known to cause or contribute to disease. We can find gene variants that are known NOT to cause or contribute to disease, meaning that they are normal variations of the genome. We can find gene variants that are novel and of uncertain clinical importance, meaning that we do not know if they cause or contribute to disease or if they are normal variations of the genome.

2. Most of the results that are important to your child's or your family's health and/or the health of you/your relatives fall in the first category, i.e., gene variants that are known to cause or contribute to disease. If we find one or more of these gene variants in your child's DNA sample, it could be that: the gene variant has already caused health problems or may cause health problems in the future. Identifying gene changes that are not related to the disease being studied (i.e., SMS) are known as **incidental medical information**. We will find gene changes in everyone that we study, but we are only specifically looking for genes related to the disorder (SMS) being studied.

3. If we **find a** gene variant that has health implications, we will repeat the test for that specific gene variant in a clinical laboratory, i.e., one that is approved for supplying genetic information to patients. We will **only** give you results about specific abnormal gene variants that we think are important to your child's or your family's health, that have been confirmed in a clinical laboratory.

4. In the future, we may contact you by mail or phone to find out if you are interested in learning about these results or gene variants that are important to your child's health and/or family's health. We may also contact you to find out if you are interested in having additional clinical tests and evaluations at the NIH Clinical Research Center.

5. You will be given a choice to **learn or not to learn** the results of your/your child's genome sequencing. You may “opt out” of learning these results, and still be in the study. (The only exception to opting out is if we find a result that has **urgent** importance to your/your child's health. We plan to share this type of result with you. However, you should know that this type of result will be found rarely, and most people in this study will not have a result
In addition to knowing what we could find, we would like you to know the limitations of the genome sequencing and what we will not be able to tell you about the changes that we find.

1. Not all gene changes that cause disease will be detected.
2. Some changes that are not currently known to cause health problems will be found to cause health problems in the future. We cannot promise to be able to tell you about those changes in the future.
3. We will not tell you about gene changes that are not known to have health implications.
4. This gene sequencing cannot be substituted for diagnostic testing recommended by other physicians.

Research using genome sequencing may take years. Initially only summary results will be available. However, we may detect a genetic change that could be the associated with your child’s disorder. Also, science changes quickly, and we may learn more about the human genome after we discuss the initial results. If we think this new information is important to your child’s or your family’s health, we may re-contact you. If we do detect an important genetic change, and you want us to tell you about it, then we will have to confirm the result first in a clinical testing laboratory. Please let us know your preference by initialing one of the statements.

____ I would like to be contacted with information about the progress of this study and contacted about any results that might be related to my child’s disorder being studied. I understand that this research will take years and that a specific cause might not be identified in my child. [For us to contact you, you have to keep us up to date on your current address and phone number.]

____ Please do not contact me regarding the progress of this study or any specific gene change you found.

To facilitate future genetic research, your child’s DNA sequence information may be deposited in NIH controlled public databases in a manner that would not allow someone to identify your child. Please understand that this information cannot be removed once it is deposited.

**FUTURE USE OF YOUR DATA**

As part of this study, we will be collecting and storing biological specimens that include, but are not limited to DNA, RNA, blood, tissues, cell lines, as well as urine and/or salivary samples. While we may do some testing immediately, we may store your child’s samples in the freezer in Dr. Gahl’s laboratory for future use. In addition, we will store certain clinical information (phenotypic data) in password protected electronic dataset. We may be interested in sharing your/your child's samples to pursue research related to SMS and similar genetic disorders. This may involve sharing clinical (phenotypic) data and/or samples with other investigators for use in ethics committee approved general research projects (with appropriate confidentiality protections). If we do so, we will not reveal your (your child’s) identity, but there will be a code to link your/your child’s data and/or sample(s) with her/her name and other personal information. The code key will be kept in a separate file from identifying information and stored in a locked cabinet under the control of Ann Smith, Adjunct PI and/or Dr. Gahl’s laboratory.

**WHAT ARE THE RISKS OF THE STUDY?**

Possible risks and discomforts you could experience during this study include:

**Blood collection:** There may be minimal discomfort involved with blood collection. A numbing cream will be applied prior to blood draws to reduce the pain associated with this procedure. There is a small chance that your child will develop a bruise or an infection at the needle site, or may feel lightheaded or faint.

**Saliva collection:** There may be minimal discomfort (dry mouth) associated with collecting 3-5 cc of saliva. Collection of saliva samples at home may be slightly inconvenient.
Skin biopsy: The risks of a punch biopsy include brief pain, slight bruising, and rarely, infection where the needle (for lidocaine) and the punch went in. We take every precaution to prevent infection. Some people feel dizzy when they have a biopsy, but this goes away when the person lies down.

Surgical samples: The tissue removed during surgery would be thrown away if we did not keep it, so there will be at no physical risk if we keep the tissue.

SMS Research Packet (questionnaires): The physical risks of participating in this aspect are anticipated to be minimal. All that is required is the time to complete the questionnaires either in hardcopy or via the CTSS. Completing these takes time (estimated 1.5-2 hours) and may represent a minor inconvenience. We believe the risk of psychological harm is minimal since the families already know the diagnosis of SMS. The risks that require more serious consideration relate to keeping a person’s name in a database. Although every reasonable effort will be made to keep information confidential, there can be no guarantees that errors in protecting this information will not be made.

Emotional and Psychological Risks:
Genetic information about you and your family may be discovered during this research project. The test results may show that you or your family has a change in your genes that causes this condition. Learning about this information may cause emotional or psychological stress.

Information about the parents may be discovered in the course of this research project. In other words, issues of adoption and paternity (fatherhood) may be discovered. Our policy is not to discuss this information with you unless it has direct medical implications for you or your family.

Unanticipated medical information: During the course of this study, it is possible (although not likely) that we will obtain unanticipated information about you or your child’s health or genetic background. If this information is considered to be relevant to your/your child’s health care we will provide it either to you or your referring physician.

We will not release any information about you or your family to your insurance company or employer without your permission. There may be a risk that genetic information obtained as a result of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. If you have any questions, please ask Ann Smith (Adjunct Principal Investigator) or the Principal Investigator. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your/your child’s information.

Confidentiality and availability of genome sequence data: All DNA samples will be coded. Only medical personnel involved in this study will have access to both the participant’s name and DNA code. If we submit your/your child’s DNA sequence to a NIH controlled public database it will be done in a manner that that would not allow someone to identify your child. You need to be aware that DNA sequence is like a fingerprint. There remains a theoretical risk of revealing your/your child’s identity. We consider this risk to be extremely low, because identifying an individual based on these data would be very difficult, and because there appears to be no reason for anyone to do this.

You, your child, or a family member could be recognized if we publish a photograph, family tree, or specific details about you. We will not use your/your child’s name(s) or publish identifiable photos/video clips without asking you to sign a separate consent form for photography. Unpublished photos/video clips will be used for teaching and record keeping purposes.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

The information we collect in this study will add to our experience and knowledge about SMS. Information from this
study may help advance our understanding of what causes SMS and why children with SMS have the problems that they have. However, it is not expected that your child will receive any direct treatment benefit from participating in this study. No new therapy is offered as a part of this protocol.

WHAT ARE MY OTHER OPTIONS?

Participation in this study is voluntary. You have the right to choose whether or not to participate. Your choice will not affect your/your child’s medical care or alter the options to participate in other parts of this NIH study or other research projects.

WHAT IF I CHANGE MY MIND?

You may stop participating in this study at any time. You may request to have the blood and tissue samples and information collected about your child destroyed. Your decision about this study will have no effect on your eligibility for future NIH studies.

WHO ELSE WILL KNOW THAT I AM IN THIS STUDY?

The personal information that you give us during the course of the study will remain confidential. All information about your child will be kept in locked cabinets or password protected computer files. Biological specimens obtained during the course of our research will be coded and stored in a freezer for future use. Only members of the SMS Research Team will have access to the data and biological specimens. There will be a code to link your child’s clinical (phenotypic) data and biological specimens with his/her name and other personal information. The code will be stored in locked file cabinet under the control of Ann Smith, Adjunct PI and/or in Dr. Gahl’s laboratory.

WILL I RECEIVE PAYMENT FOR BEING IN THIS STUDY?

You will not receive payment for taking part in this study. If a cost is incurred in drawing blood and/or to perform the skin biopsy, these will be covered by the study.

CONFLICTS OF INTEREST

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](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.

This protocol includes 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.
CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

MEDICAL RECORD

• Adult Patient or  • Parent, for Minor Patient

STUDY NUMBER: 01-HG-0109

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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 William A. Gahl, M.D., Ph.D. or Adjunct Principal Investigator, Ann C.M. Smith, M.A., CGC, Building 10, Room 10C103, Telephone: (301) 435-5475. Other researcher you may call is: Medical Advisory Investigator Wendy Introne, MD, Building 10, Room CRC 3-2541, Telephone (301) 451-8879.

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.

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<tr>
<th>A. Adult Patient's Consent</th>
<th>B. Parent's Permission for Minor Patient</th>
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<td>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.</td>
<td>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.)</td>
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Signature of Adult Patient/Legal Representative Date

Signature of Parent(s)/Guardian Date

Print Name

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 JUNE 30, 2015 THROUGH JUNE 29, 2016.

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

NIH-2514-1 (07-09)
P.A.: 09-25-0099
File in Section 4: Protocol Consent