INSTITUTE: National Human Genome Research Institute

STUDY NUMBER: 14-HG-0071 PRINCIPAL INVESTIGATOR: Carlos R. Ferreira, M.D.

STUDY TITLE: Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation

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Standard

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 ("you" throughout this consent refers to you or your child) have been referred to the National Institutes of Health because you show signs of having a disorder affecting the sugars, proteins, and fats in your body. Your doctors suspect that you might have a congenital disorder of glycosylation (CDG), meaning that you were born with a defect in "glycosylation," which is the process of attaching sugars to proteins and fats. Protein and fat molecules are found throughout your body and perform a number of functions to keep your body working properly. Many protein and fat molecules have sugar molecules attached to them for a variety of reasons, including directing the proteins and fats to their proper places in your body, stabilizing their shapes, and even helping the proteins and fats do their jobs. It is estimated that half of all of the proteins in our body are glycosylated and 2 percent of our genes that encode proteins are known to participate in glycosylation reactions.

Because of the complexity of the glycosylation process and how widespread it is in humans, patients with congenital disorders of glycosylation can have a range of physical and health problems. Problems commonly seen in many congenital disorders of glycosylation include poor growth, learning disabilities, having a higher risk of getting infections and a harder time fighting off infections, skin abnormalities, muscle weakness, and deposits of fatty tissue (fat pads) in unusual places in the body, as well as other problems. There are no known cures for these conditions and treatment depends on the type of CDG and accompanying medical problems.

The purpose of this study is to gain a better understanding of the medical complications of CDGs in a large number of patients and to gain a better understanding of what causes these complications. We also hope to identify genes associated with CDGs. We are especially interested in identifying certain characteristics of these disorders, which may help in the design of new therapies in the future.

WHAT IS INVOLVED IN THE STUDY?

Your participation in this protocol may last for as long as five to 10 years, unless you decide not to continue in the study or the NIH ends the study ahead of schedule. Patients entering this study will be admitted to the National Institutes of Health Clinical Center for an evaluation every two years. Before your first visit to NIH, your doctor will be asked for results of blood tests that confirm that your child has one of the CDGs we are studying in this protocol. The visits at the NIH Clinical Center will last three to five days. During or before these admissions you will be asked to sign a release of medical information so that our research team can obtain your medical records from doctors. With your permission you will be seen here by doctors, nurses, and counselors from several fields. Any tests or evaluations performed as part of this study will be fully explained to you, and you are free to refuse any test. Some of the procedures have risks associated with them and will require a separate consent form.

Listed below are the examinations, procedures, and tests that you will have for the research part of the study, unless you refuse or the investigators determine that there is a medical reason for you not to have a test.

-We will obtain a complete medical and family history and perform a physical examination.

-We will ask you to complete a questionnaire regarding your (or your child's) prenatal, birth, newborn, and past medical history, family history, growth and development, nutrition, medications and therapies.

-We will collect blood samples:
Blood samples will be drawn to check your nutritional status and the health of your liver, kidneys, pancreas, bone marrow, immune system, inflammatory system, clotting system, and endocrine system. Some blood will be stored for future research. A blood sample will be sent to our research collaborators who are also studying CDGs. The blood that is sent to research laboratories will be sent without your name or any other identifying information about you. You will not receive the results of any testing performed in a research laboratory.
If you have not already had testing for the particular genetic changes (mutations) that cause your CDG then a sample of blood may be sent to a CLIA-certified clinical laboratory for genetic testing. CLIA stands for the Clinical Laboratory Improvement Amendments, which apply to all clinical (not-for-research) laboratory testing. CLIA-certified laboratory testing is regulated by the Centers for Medicare and Medicaid Services, an agency of the U.S. Department of Health and Human Services (HHS). This sample will be sent with your name on it and the results of the test will be communicated to you.

The amount of blood drawn for children will be no more than 5 mL of blood (1 teaspoon) for every kilogram (about 2 pounds) of body weight in a single day, and no more than 9.5 mL for every kilogram may be drawn over any eight-week period. This is considered to be a safe amount for children, according to NIH guidelines. For adults we will not exceed 10.5 mL (2 teaspoons) for every kilogram of body weight or a total of 550 mL in an 8-week period, according to NIH guidelines. If you are being treated for a seizure disorder, blood will also be obtained to check the level of anti-convulsant medications.

-We will collect urine samples:

We will collect urine to study your kidney function, pregnancy status if you are a female and between menarche and menopause, and urine sugar profiling. Some urine will be obtained for research. Any urine that is sent to research laboratories will be sent without your name or any other identifying information about you. You will not receive the results of any testing performed in a research laboratory.

For children or adults who are not toilet trained, or who are incontinent, we will use a bag to collect the urine. This bag is attached to the skin by an adhesive strip. Cotton balls placed in diapers may also be used to collect urine samples.

-We will perform a skin biopsy:

-This procedure will be done only once at the initial visit on all subjects. If you refuse this study, it will not affect your participation in the rest of the research protocol. A second skin biopsy may be done only if the first sample is suboptimal. The procedure involves numbing the skin with either a topical or local anesthetic. Once the area is numb the skin will be cleaned with alcohol and a 3 or 4 millimeter (1/8 inch of the size of a pencil eraser) circular area of skin is removed using a punch and scissors. This biopsy is done under sterile conditions and takes approximately five minutes. Skin cells (called fibroblasts) will be grown from the skin biopsy and will be used to study genetic and biochemical aspects of CDGs. Fibroblasts will also be frozen and stored for future use. Cells may also be sent to other research laboratories collaborating on this project. If this is done the cells will be transferred without your name or any other information that will identify you directly. This is called a de-identified sample.

-In a subgroup of patients, we will try to grow some of the cells removed by the skin biopsy and modify them in the laboratory to make them into "induced pluripotent stem (iPS) cells." ~~These are recently discovered special cells that you may have heard about in the news.~~ They can form any type of cell in the body and may be grown in the laboratory in a flask or dish forever. This is often necessary because the specialized cells that are defective in certain diseases cannot be obtained from patients without extremely invasive procedures. For example, nerve cells cannot be obtained from the brain and vascular cells cannot be obtained from arteries without great risk to the patient. These cells, however, can be made from skin cells obtained from a relatively benign skin biopsy. In a manner similar to embryonic stem cells, iPS cells have the potential to originate all cells of the body, but because they are derived from adult tissues (generally skin cells), they do not require the destruction of embryos for their generation.

-We will do an ophthalmology (eye) exam:

An eye doctor will perform a complete eye examination.

-We will perform radiology tests:

-Hand and wrist X-rays will be performed if you are less than 21 years old to determine bone maturity.

-We will perform a baseline Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS):

MRI is a safe procedure that does not use any radiation (such as X-rays). The MRI study will allow us to get pictures of your brain. For the MRI scan, you will lie on a stretcher that is moved into a cylindrical machine. Because MRI uses a strong magnetic field, metal objects in the body can cause a problem. You may not be able to participate in this study if you have any of the following: cardiac pacemaker, neural pacemaker, cochlear implants, surgically implanted metal (magnetic) plates, screws or pins, surgical clips in the brain or on blood vessels, or metal (magnetic) objects in the body, especially the eye. Please inform us if you have any concerns or questions about this. This study may be repeated annually if indicated.

-We will obtain an ultrasound of the abdomen to see changes in the kidneys, liver, spleen and portal blood vessels and possibly other tissues. This will include a specialized form of ultrasound called Doppler, which will help determine the direction of the blood flow in the portal vein.
-We will obtain a Fibroscan of the liver to look for fat deposits or scar tissue called fibrosis specifically in the liver.
-We will also perform ultrasound of the heart (also called an echocardiogram). For the ultrasound evaluation, a probe held on the skin sends sound waves to organs and a computer converts the sound waves that come back from the organs into images. This is painless and there is no exposure to radioactivity. These results help confirm the diagnosis and might change the clinical management of your/your child's condition. These studies may be repeated annually if indicated.
-We will obtain a bone density scan (sometimes called a DEXA scan). The DEXA scan measures body fat, muscle, and bone thickness. This procedure involves lying on a flat table while a very small dose of X-rays are passed through the body. The total time required to stay in the imager will be determined by the doctor performing the examination, but we estimate this will take, at most, 30 minutes. At all times, you will be able to communicate with the technologist operating the machine and others in the room. You may come out of the imaging device at any time. There is no discomfort or physical pain involved.
-We will perform an electrocardiogram where electrodes are placed on the skin of the chest through an adhesive, and non-invasively measures and records the electrical activity of the heart.
-We will perform a hearing evaluation and test. The hearing test is performed by an audiologist in a soundproof room, if possible, using sophisticated calibrated equipment.
-We will perform Neuropsychological Testing:
Because the CDGs produce degeneration in your ability to think and remember, you will undergo testing to assess your cognitive or thinking abilities. This test may take one to three hours depending on your cognitive ability. Parents or caregivers will be asked questions about your development. ~~The results of these tests will be made available to you.~~
-You will have initial consultations with several specialists including a physiatrist (physician specializing in rehabilitative medicine), physical therapist, occupational therapist, neurologist, ophthalmologist, audiologist, immunologist, endocrinologist, hematologist, hepatologist, developmental specialist and nutritionist.
-We will photograph and videotape you:
Taking photographs of your face and body will help us track growth and appearance. We may also videotape you to document your movements and overall mobility. These photographs will only be shared with members of the research team. If we want to publish a picture of you we will ask for your specific written permission. You may decline to have your photo published.
-If not performed previously, we may perform genetic analyses:
-DNA will be obtained from your blood or cells and kept indefinitely, or until such a time that the investigators decide to destroy your genetic material. Your condition is likely to be caused by an abnormality of a specific gene. Every cell in the body has many genes that together are like a computer program that controls the cells of the body. If one gene does not work right, the whole cell may not work right, just like a damaged computer program. The genes are all together in several very big molecules called DNA. In your DNA, genes known to cause CDGs will be analyzed. In addition, other genes may be studied to try to find new genes responsible for CDGs, or to improve our understanding of these diseases. Some of these studies may be performed outside of the NIH. If the studies will provide useful information that can be reported to you (for example, a test for a gene known to cause CDGs), samples will be sent to clinical testing centers with identifying information. Other tests related to the diagnosis or understanding of CDGs may be performed on your sample, without any information that identifies you. They will be coded so that the outside investigator will have no way to know to whom these materials belong.

-We will provide information to you about results of tests that are part of regular medical care, such as studies that might be available in a regular doctor's office or hospital. We do not plan to provide you with the results of any research data or results because further research may be necessary before these results are meaningful. If meaningful information is

developed from this study that may be important for your health, you will be informed when it becomes available. If the information learned in this study may be important to you or your family's health, we will contact you to discuss this information with you.

-We may use new techniques called "genomic sequencing" to look for the causes of CDGs by looking at many genes at once. In using these techniques to find the causes of CDGs, we may also find genetic changes that have to do with other health issues not related to CDGs. If these genetic changes are felt to be urgently medically significant, we will confirm our findings, and will let you know what we have found. By "urgently medically significant", we mean that these changes have immediate health implications for you or your family, and that there is an intervention or treatment that would be helpful. An example of this would be a change in a cancer-related gene that would mean that it would be important to be examined to check for cancer. Once the gene change is confirmed, we will discuss the results with you and make recommendations regarding appropriate medical follow up. The NIH can not promise to perform or pay for recommended medical tests or evaluations.

-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 can not promise to be able to tell you about those changes in the future. However, we will attempt to contact you if we do learn about something that is of potential clinical significance.

3. We will not tell you about gene changes that are not known to have health implications.

4. We will not tell you about gene changes that predict a person has or will develop a severe disease for which there is no treatment or any specific intervention available.

5. This gene sequencing can not be substituted for diagnostic testing recommended by another physician.

- We are required to deposit your genomic sequencing data and some clinical information into a database. Once deposited into this database, the genomic data will be used only for health-related or biomedical research purposes. Access to this database is limited, and researchers who use it must promise to keep the information confidential. The information that we deposit will not include your name or similar identifiers.

The following examinations, procedures, and tests will be considered only if there is a medical reason to perform the study.

-Additional blood tests to study in more depth your immune system, endocrine system, clotting system, and nutrition may be obtained if a problem is suspected.
-Additional urine tests may be obtained to study your kidney function in more depth if a problem is suspected.
-Stool may be obtained to study your gastrointestinal and nutritional systems if there are signs of dysfunction like chronic diarrhea or poor growth.
-We may perform a speech/language evaluation:
Because CDGs can impair your ability to speak, you will receive an evaluation by a speech pathologist. We will be collecting data on your speech, oral motor function, and swallowing problems. This will involve meeting with a speech pathologist, answering questions, and having an examination of your oral motor function.

-We may perform a lumbar puncture (spinal tap) if there are indications of unusual seizures, development, or other neurological symptoms:
As part of the CDGs the brain may produce chemicals or proteins that indicate the nervous system is stressed. In order to study these proteins it is necessary to obtain spinal fluid from you. The fluid is obtained by performing a lumbar puncture or spinal tap. If you require sedation for the MRI/MRS the spinal tap will be performed while you are sedated. The spinal tap will be performed using numbing medication applied to the skin over your lower back. Local anesthetic to numb below the skin will be injected in the area of the back where the procedure will be performed. After cleaning the area with antibacterial solution, a thin needle will be inserted into the spinal canal in your lower back and 1-2 teaspoons of the clear fluid that surrounds the spinal cord will be sampled. You will be asked to sign a separate consent form for this procedure and be given the chance to ask additional questions at that time.
-We may perform a pulmonary function test if we suspect problems with your breathing:
This test measures your lung function by having you breathe into a tube attached to a machine.
-We may perform a skeletal survey if there are indications of problems with your bones such as history of fractures, growth failure, boney deformities, or other such signs and symptoms: A skeletal survey is a series of x-rays of all the bones in the body. This test usually takes between one to two hours.
-We may perform an electroencephalogram (EEG) if there are symptoms suggesting developmental/neurological problems:Patients with CDGs may develop seizures during the course of their disease. Sometimes the seizures are detectable only by doing a brain wave test called an electroencephalogram or EEG. To do this test small discs, known as electrodes (small pieces of metal attached to wires) will be placed at specific sites on your head. The electrodes can detect the natural electrical activity (brain waves) of your brain. Before the electrodes are placed, the site will be cleaned with an alcohol swab. A paste is then used to attach the electrodes. Your brain waves will be recorded when you are resting quietly. This study may be repeated annually if indicated.

-We may perform an electromyogram and nerve conduction studies if there are problems with weakness or movement:
A nerve conduction study (NCS) is a test that measures the speed and strength of electrical activity in a nerve. The test can gather information about the structure and function of both muscle and nerve. Your skin will be cleaned. Electrodes will be taped to the skin along the nerves that are being studied. Your doctor will use a small stimulus to apply an electric current that causes the nerves to activate. The electrodes will measure the current that travels down the nerve pathway. If your nerve is damaged, the current will be slower and weaker. The stimulus will be placed at various locations to determine the specific site of the damage. Needle EMG is performed by inserting a needle containing a recording electrode into the muscle of interest. The muscle is evaluated at rest and with action. The number of nerves and muscles tested depends on the suspected underlying condition and is decided on a case-by-case basis.
-We may perform a auditory brainstem response test (ABR) if recommended by the audiologist:
The ABR is another test used to measure hearing in young children or in individuals who cannot cooperate with a traditional hearing test. To do this test, small electrodes will be placed at specific sites on your head similar to those placed for an EEG as described above. After the electrodes are placed, your brain waves will be recorded when a sound stimulation is given.
-We may perform a sleep study if you have been having difficulty sleeping: During the sleep study, your brain waves, the oxygen level in your blood, heart rate and breathing, as well as eye and leg movements are recorded through electrodes while you sleep.

-We may perform a videofluroscopy if you have problems with swallowing or choking: A videofluoroscopy studies your swallowing by taking an X-ray motion picture of the way you swallow different textures of food. The full evaluation will take approximately 1 ½ hours. With your permission, the results and recommendations arising out of this evaluation will be made available to your speech therapist.

-We may perform additional ophthalmologic studies if suggested by the ophthalmologist: Photographs of the retinas of both your eyes may be taken with a special camera at each exam. A test that looks for problems in the brain that affects vision called a electroretinogram may be performed. It involves flashing lights and recording brain waves related to the nerves that make up the visual pathway. Optical coherence tomography (OCT) may be used to assess retinal health.
-We may perform a muscle biopsy: If our examination or tests show that the muscles are involved in the disease process, we may ask you to undergo a muscle biopsy. A muscle biopsy involves taking a piece of muscle, usually about 1 inch wide, from the front part of the thigh. This is usually done under general anesthesia. Taking the piece of muscle will leave a small scar on the thigh.
-You may have additional consultations with dermatology, cardiology, pulmonary, gastroenterology, dermatology and dental if you are experiencing any problems with any of these systems. Follow-up consultations with any previously seen specialist may occur if needed.
-Sedation may be used during procedures requiring prolonged immobility, pain, or discomfort if the risks of the sedation and procedure do not outweigh the benefits gained by having the study results. Such studies may include MRI/MRS, ABR, spinal tap, electromyogram and nerve conduction studies, electroretinogram, and muscle biopsies. Sedation in children may be initiated only for clinically indicated procedures, but if a child is sedated for a clinically indicated procedure, other research procedures that require sedation may be added on. Consent will be obtained prior to all procedures performed under sedation. Prior to anesthesia, you will also have a pre-anesthesia assessment by the anesthesia team. You will be informed of what will happen during the sedation by the anesthesia team during that visit. This will give you a chance to ask questions. You will also be asked to sign a separate consent form for the sedation.

-Additional unanticipated studies that would benefit your health management may be performed or recommended based upon the judgment of the members of the medical team.
-We will discuss all your medical test results and evaluation reports with you at the end of the visit. You will receive a copy of all your test results and consult reports. We will not tell you the results of our research testing unless it has been verified in a certified clinical laboratory. If you do not want to have one or more of these medical tests, let the research team know. All tests may not be required for every patient, and you may still be able to participate in the remainder of the study. By agreeing to participate in this study, you do not waive any rights regarding access to and disclosure of your records. Medical test results provided to your physician will become part of your medical record.

FUTURE USE OF YOUR DATA/BIOLOGICAL MATERIALS

In the course of our research, we will obtain blood, spinal fluid, urine and tissue samples. While we can do some of our tests immediately, we will store some of your samples indefinitely in a locked freezer for future use. In addition, we will store certain information in your NIH medical record. We, as well as other researchers within and outside the NIH, may be interested in using your blood, spinal fluid, DNA samples, urine, cell lines or tissue samples to pursue other research projects related to your disorder. If we share your samples with other researchers, we will not reveal your identity, but there will be a code to link your samples with your name and other personal information. The code will be stored in a locked file cabinet under the control of Drs. Ferreira, and Gahl.

In the case of the cell lines (fibroblasts and iPS cells) generated from the skin tissue biopsy or from other cells of your body, it is possible that these samples will be shared with other investigators for use in ethics committee approved general research projects other than those involving your disorder. Examples of future basic research uses include genetic modification of cells, large-scale genome sequencing, and patenting of scientific discoveries.

Samples will be shipped to other laboratories in a way that no individual can be identified from the samples. Your sample will be coded, i.e. it is not possible to identify you through the traditionally used identifiers i.e. name, address, telephone

number, or personal identification number. These cell lines will be stored and used by both study investigators and other investigators after the completion of their respective studies, which can extend for many years."

The cell lines will not be sold to other researchers. Although it is possible that the cell lines generated from the tissue samples will have commercial potential, you will not receive financial benefits resulting from future commercial developments and/or patents issued based on research with cell lines generated from your tissues.

The iPS cells will not be used for cloning or to grow artificial organs or organisms. They will not be used in reproductive research.

In the event that you withdraw your consent to participate, your tissues samples will be destroyed but the cell lines generated from the skin tissues will NOT be destroyed. The development of cells lines, and especially iPS cells, requires a big commitment by the investigators in terms of time and cost. Elimination of such lines could seriously affect research, as these lines are not readily replaceable. Furthermore, these cell lines may be shared with other investigators and re-contacting all recipients of the cell lines made from your samples may not be a feasible task. If you are uncomfortable with the cell lines created from your cells not being destroyed, you can decline to participate in this aspect of the study.

In addition, it is possible that some information obtained from these studies will be published in the medical literature. However, your identity will not be included in these publications.

WHAT ARE THE RISKS OF THE STUDY

Blood collection and IV placement
There may be some physical discomfort when we collect your blood with a needle and place an IV line. There is a small chance that you will develop a bruise, feel lightheaded, or faint. There is a very small chance that you may develop an infection at the needle or IV site.

Urine collection
For a child who is not toilet trained, or an adult who is incontinent we will use a bag to collect the urine. This bag is attached to the skin by an adhesive strip. Similar to the removal of a Band-Aid, the removal of the urine bag can be uncomfortable.

Skin biopsy
The risks of this procedure include a reaction to the local anesthetic (very rare), local bleeding (occasional, but easily treated), and infection (rare). There will be a small scar (about ½ the diameter of a pencil eraser) at the biopsy site. Discomfort at the biopsy site is usually mild and goes away in a few minutes. This discomfort can be treated with minor analgesics such as acetaminophen. The wound generally scabs within 3 days and heals in 7 days.

Muscle biopsy
The risks of this procedure include a reaction to the generalized and local anesthetic (very rare), local bleeding (occasional but easily treated), and infection (rare). There will be a small scar at the biopsy site. Usually the scar is small and nearly unnoticeable, but sometimes a raised scar or visible lump may result. Discomfort at the biopsy site is usually mild and can be treated with minor analgesics such as acetaminophen. The biopsy site will be covered by a dressing and you will receive instructions on how to care for the area.

Ophthalmologic (Eye) exam
The light used to examine the eyes can be bright and can cause mild discomfort. Dilation of your pupils may cause some temporary glare and blurred vision. Occasionally there may be a local allergic reaction to the medication used to dilate the eyes. If this should occur, medication to control the allergic reaction will be given to you.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS)
MRI and MRS are safe procedures that are widely used in medical practice. The risks are related to having a magnetic metal device in place that goes undetected before the study is started, and the discomfort of remaining still in the scanner for an extended period of time.

Sedation
The risks of sedation include decreased rate of breathing while under sedation and aspiration (saliva or stomach contents breathed into the lungs). Additional risks include a drop in heart rate or blood pressure. In the rare event that this should occur, the anesthesiologist may have to put a longer breathing tube into your mouth and windpipe, use a respirator to breathe for you, and give medications to raise your blood pressure. If you have a severe reaction during the sedation procedure you will be resuscitated regardless of whether or not you have made plans not to be resuscitated under normal circumstances. Please inform us if you or a family member has had problems with sedation or anesthesia in the past.

Radiation Safety Related to DEXA and Bone Age X-ray
This research study involves exposure to radiation from a DEXA scan for subjects who are able to remain still for the duration of the scan and a bone age x-ray for children under 18 years old. Please note that this radiation exposure is not necessary for medical care related to you or your child and is for research purposes only. The total radiation exposure in this research study is estimated to be 0.046 mrem. This dose is well within the recommended radiation exposure limit for child volunteers (500 mrem/year) or adult volunteers (5000 mrem/year) as set by the NIH Radiation Safety Committee. For comparison, the average person in the United States receives a radiation exposure of 300 mrem per year from natural sources, such as from the sun, outer space, and the earth's air and soil. The dose that will be received yearly from this research study is less than the amount normally received in 1 day from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects, which can be obtained online at http://www.genome.gov/Pages/Research/Intramural/IRB/ResearchPatientBrochure.pdf.
While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). Therefore, the total risk of fatal cancer may be estimated to increase from 25 percent to 25.01 percent. This additional risk is too small to be measured and is generally regarded as insignificant.
Please tell us if you or child have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you or your child will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into the body.
If you are pregnant you may not participate in this study as the fetus is more sensitive to radiation than children or adults.

Electroencephalogram (EEG) and Brainstem Auditory Brainstem Response (ABR)

Electrodes attached to your head with medical paste may cause mild discomfort. The electrodes will be removed after the test and the residual electrode paste may remain in your hair temporarily. Washing and combing may be required to remove it.

Electroretinogram
This test involves flashing lights along with the recording of brain waves. The flashing lights may produce minimal discomfort. In addition, certain individuals may be at risk for experiencing a seizure in response to the flashing lights.

Spinal Tap
A spinal tap is a relatively safe procedure and is performed routinely in very young children if they are evaluated in an emergency room for an unexplained fever. Complications that can occur following a spinal tap include leakage of fluid when the needle is withdrawn (occasional but usually stops on its own within minutes) or an infection at the needle site (rare). Very rarely bacteria from the skin could be carried on the needle and infect the spinal fluid, a condition called meningitis. There is also a very small risk that bleeding around the spinal cord could occur. Some adults who receive spinal taps have headaches after the test. We do know if this also occurs in young children. After the spinal tap you will be allowed to recover from the sedation and resume your normal routine. No other special precautions related to the spinal tap are necessary.

Nerve Conduction Study and Electromyelogram
Although rare, bleeding is a potential complication with needle EMG. Subjects may experience some pain and discomfort during the procedure. Small bruises or swelling may develop at some of the needle sites. The needles are sterile, so there is very little chance of getting an infection.

Genetic evaluations
Genetic information about you and your family may be discovered during this research project. Issues of adoption and parentage may be discovered in the course of this study. It is our policy not to discuss such information with you unless there are direct reproductive or medical implications for you or your family. There may be a risk that genetic information obtained as a result of participating 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 a member of the research team. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your information.

Neuropsychological test /Cognitive (learning) tests
There is no discomfort or risk associated with the cognitive (learning) tests. However, younger children may find the tests boring and stressful.

Medical photography and videotape
Taking photos and/or videotaping may be embarrassing to some patients.

Emotional and psychological risks
Emotional and psychological risks are also possible. It is possible that learning you have a gene variant that causes or contributes to your medical condition could lead to emotional or psychological harm. Family information such as parentage and adoption may be found in this research project. It is **not** our practice to disclose this type of information unless it has direct medical implications for your family.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

No specific therapy will be given to you while you are participating in this study therefore it is likely that you will receive no direct benefit as a result of participation in this study. However, the testing and expert evaluation you receive may reveal medical problems that were previously unrealized and thus benefit you indirectly. The data collected in this study will add to our knowledge of CDGs. Information from this study may help advance our understanding of what causes the CDGs and why patients with these diseases have the problems they have. This increase in knowledge and experience may benefit other patients with CDGs in the future. Therapies might arise in the future based on this protocol, but we do not have new therapies to offer at this time.

WHAT ARE MY OTHER OPTIONS?

You do not have to participate in this study if you do not want to.

WHAT IF I CHANGE MY MIND?

You may stop participating in this study at any time. If you request to have your DNA, and blood/urine samples destroyed, we will to the best of our ability identify all of your research samples and destroy them. However, we may not be able to destroy samples sent out to other researchers, though we can request that they destroy your samples according to your wishes. We may not be able to destroy the cell lines derived from your skin samples. You may also request that your photographs be destroyed, and they will be. It is possible that some of the genetic variations found in your DNA may be submitted to on-line genetic databases. Such on-line database information can not be withdrawn.

WHO ELSE WILL KNOW THAT I AM IN THIS STUDY?

The DNA and blood/urine samples we collect from you may be shared with other researchers in the future, linked together with other information such as your age, gender, and ethnicity. Similarly, we might share your clinical and/or laboratory data with other researchers. We will share such samples and data, but we will not give other researchers your name, address, or phone number. There will be a code to link your samples with your name and other personal information. The key to the code will be kept locked in Dr. Ferreira/Gahl's offices and will be accessible only to the NIH investigators. We may publish a chart that shows your family tree and who is affected, but we will not use your family's name. If you have a unique family others may still be able to recognize the family tree.

WILL I RECEIVE PAYMENT FOR BEING IN THIS STUDY?

You will not receive payment for taking part in this study.
It is possible that studies using your DNA or blood/urine samples may enable researchers to develop medical tests or treatments that have commercial value. You will not receive any money that may result from such commercial tests or treatments.

CONFLICT 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. You may ask your research team for additional information or a copy of the Protocol Review Guide."

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 Carlos Ferreira, Building 10, Room 5D38. 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. 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 _____

C. Parents' 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/Guardian _____ Date _____

Print Name _____

Signature of Parent/Guardian _____ Date _____

Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 13, 2017 THROUGH AUGUST 12, 2018.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____