

Informed Consent Document

TITLE OF RESEARCH: Genomic Diagnosis in Children with Developmental Delay

IRB PROTOCOL: X130201001

INVESTIGATOR: Dr. Martina Bebin

SPONSOR: National Human Genome Research Institute of the National Institutes of Health (NIH)/ HudsonAlpha Institute for Biotechnology (HudsonAlpha)

For Children/Minors (persons under 19 years of age) participating in this study, the term *You* addresses both the participant ("you") and the parent or legally authorized representative ("your child").

Purpose of the Research

We are asking you to take part in a research study. In this research study we are trying to determine if new technologies that look at people's DNA can explain why some children have problems with the development of their brain and body. We also want to understand if, and how, families like yours find that information helpful.

Additionally, we are trying to find out how to best handle other information, termed "secondary findings", that may be discovered at the same time we are searching for information related to your child's condition. For example, we might learn that you are at a higher risk of developing heart disease or getting cancer, and it is important to know if and how to communicate that information.

Unlike standard genetic testing, this study will look across all of your DNA, rather than looking at only one or a few places in your DNA. For example, one technique that we may use is called "exome sequencing", a strategy that involves analyzing all of the genes in a person's DNA, which are among the most important functional parts of our genetic information. Exploring the benefits and challenges of such comprehensive genetic testing is the key goal of this study. This study will enroll 600 participants with developmental delays and 1200 parents of these participants at Dr. Bebin's North Alabama Children's Specialists (NACS) in Huntsville, Alabama.

Explanation of Procedures

If you agree to participate in this study, you and/or your child's other parent, will:

- Give us permission to comprehensively analyze your DNA and assess the health relevance of the results.
- Give us permission to return information that we believe to be medically relevant to you and your child. You will have the ability to decide what specific types of information you wish to receive.
- Provide a sample of blood (8.5ml or approximately 1.7 tsp)

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- Answer some questions about you and your child, now and after you get the results of the blood test.

If you agree to have your child participate in this study, your child will:

- Assent, if they are able, to participate in this study.
- Provide a sample of blood (8.5ml or approximately 1.7 tsp)

Your blood samples will be labeled with unique codes and sent to researchers at the HudsonAlpha Institute for Biotechnology, a non-profit genetics research center located in Huntsville. Some basic information about your child's health will also be given to the research staff at HudsonAlpha.

We will use state-of-the-art technologies to generate large catalogs of information about the DNA from you and your child. A group of experts, including medical doctors, researchers, bioethicists, and your child's doctors, will use scientific findings and genetic databases to help decide what DNA information is relevant to the health of you or your family. All results found by this group to be medically relevant will be validated by an independent lab at Emory Genetics Laboratory. We expect the entire DNA analysis process to take 4 to 6 months.

If we are unable to perform analysis of your samples, we will let you know within 6 months. Budgetary and technical limitations are likely to prevent us from testing all enrolled families. There is no cause for concern if you are told that we could not complete the analysis and provide you with results.

If and when genetic results are ready, you will be scheduled for a visit with Dr. Bebin and a certified genetic counselor. We will not provide or discuss any results over the phone. At your appointment, you may be provided with:

- Primary finding: whether there are any changes in your child's DNA that have affected his or her development.
 - Most families will not receive a primary genetic diagnosis. If no diagnosis is found, we will share that information with you. Even if we do not find a genetic diagnosis, your child's condition may still be the result of a change in his or her DNA that we are unable to identify.
 - If your child receives a genetic diagnosis, this may not change the prognosis or medical treatment for your child. However, it may help both you and your child's doctor to better understand the cause of your child's condition and the risks of a similar condition affecting future children.
- Secondary findings: whether any other genetic changes relevant to your health or your child's health were found. Secondary findings may include:
 - Whether there are any changes in the DNA that could put you at higher risk for developing an unrelated disease in the future, such as cancer or heart disease.
 - Some of these diseases may have actions that can be taken to prevent or treat the disease ("medically actionable")
 - Some of these diseases do not have any known prevention or treatment strategies (not medically actionable).

- Whether you are a “carrier” for a genetic change that may cause an unrelated disease in your current or future children.
- Whether there are any changes in your DNA that may significantly alter your sensitivity to certain drugs.

You will be given the option to receive or decline secondary findings of different types and for various diseases. You will have the ability to make these choices separately for you and your child. There are both benefits and risks, described below, to receiving genetic results that you should consider when deciding.

Only a subset of results found to be medically relevant will be available for return. We will not provide you with all the genetic information that we generate.

The DNA tests we will perform can identify who is or is not a child’s biological parent, and the value of this study depends greatly on having DNA from both biological parents. We are less likely to discover diagnostic information about your child’s condition without both biological parents. If you participate and you or the child’s other parent is not a biological parent, we will not reveal this information to you, your child, or the child’s other parent. If you think you or your child’s other parent may not be a biological parent, you might not want to participate.

After you get the results of the genetic testing, which will happen in 4 to 6 months, we will ask you to complete a questionnaire at home. We may also call you to check on you. We will ask some parents to come back so we can interview them.

You will be actively enrolled in this study for less than a year total.

Risks and Discomforts

Blood Draw Risks:

The risks of drawing blood include pain, bruising, lightheadedness, and fainting. Infection at the site of the needle stick is a rare side effect. These are the same risks you face any time you have a blood test.

Confidentiality Risks:

Some of the data gathered may be shared with other scientists through scientific literature or scientific databases. We will take multiple precautions to protect the privacy of your information and decrease the risk of losing confidentiality. No personally identifiable information will be made public, nor will any researchers outside of our team have access to personal information. However, as with all research, there is a chance that the confidentiality of your information could be compromised.

Genetic Testing Risks:

The main concern associated with genetic testing is anxiety, depression, or other forms of emotional distress that may result from receiving genetic information about the risk of developing certain diseases or conditions. This is especially true for those diseases that are not

treatable or preventable. For example, Huntington's disease is a rare, debilitating, and fatal genetic disease of adulthood that is untreatable but can be predicted based on DNA information.

You may also receive information that may lead to difficult medical decisions. For example, some individuals carry DNA changes that increase their risk of breast cancer. Learning this information may result in needing to decide whether or not to take preventive measures, like surgery.

For these and other reasons, coping with genetic information may be difficult for some individuals.

It is also important to keep in mind that you and your blood relatives share much of your DNA in common. This means that genetic information about you may be important to them. For example, if you carry genetic changes that increase your risk of breast cancer, it is possible that those same changes are present in your parents, your children, and also in your extended family.

You will have the ability to decide what types of diseases and conditions you wish to receive information about, and will also be able to make those choices on your child's behalf.

By choosing to participate, you agree to receive information about changes in your child's DNA that affect his or her development. These genetic factors may be inherited from you or your child's other biological parent, even if you or your child's other parent is healthy. This information may affect the way that you view or evaluate yourself or your child's other parent. It may also influence, or generate anxiety about, future family planning decisions.

Depending on the type of genetic information returned to you, we may refer you to an additional physician or clinic for further testing and/or advice. If you experience psychological distress or other difficulties, we can also refer you to an appropriate resource for care and support.

There may be unforeseeable risks associated with receiving genetic information and the potential decisions, actions, or inactions that may result from receiving that information. Please consider this carefully and ask any questions that you may have before deciding whether or not to participate.

It is important that you consider the risks and uncertainties of this research study that make it different from traditional medical testing.

We will make sure that the information that you are given is as accurate as possible to the best of our ability. We will use the best standards, practices, and technologies available to researchers. However, the technologies available to analyze DNA and our knowledge of how DNA affects health are changing rapidly. They are also subject to much uncertainty. Some DNA changes that are important to health may be missed, and other DNA changes that are not important may be incorrectly identified as if they are. There are also moral and ethical questions

about using genetic information on which the scientific and medical communities have not reached a consensus.

We therefore do NOT guarantee the same levels of comprehensiveness, accuracy, or standardization associated with more traditional, routine medical tests.

Your consent to participate in this research must include a consideration of the risks with the return, or lack of return, of genetic information, whether or not our interpretation of that genetic information was incorrect and whether or not you or your family choose to act or not act upon that information or lack of information.

Benefits

You may find out if there is a change in your child's DNA that has altered the development of his or her brain or body. You may find out if this change could affect future children.

A genetic diagnosis may help you connect with other families in the community who face similar medical problems. Further, while unlikely, it is possible that a genetic diagnosis may point you or your child's doctor to better medical or educational treatments for your child.

You may find out if you or your child are at an increased risk for developing other diseases, and that information may be of medical benefit.

Your participation may lead to new discoveries that help to advance medical research and improve patient care in future generations.

None of the above benefits are guaranteed, and it is expected that many participating families will not receive specific information that is relevant to their health.

Alternatives

Your alternative is to not participate in this study.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of National Human Genome Research Institute, NIH and HudsonAlpha; and the Office for Human Research Protections (OHRP). The results of the study may be published for scientific purposes. These results could include your lab results and questionnaires. However, your identity will not be given out.

The following individuals will have access to your personally identifiable information: Martina Bebin, M.D., North Alabama Children's Specialists and UAB; Ed Lose, M.D., North Alabama Children's Specialists and UAB; Kelly East, M.S., C.G.C, certified genetic counselor; and Kyle Brothers, M.D., University of Louisville. Dr. Brothers may

ask you questions about your individual experiences through questionnaires, in-person interviews, or telephone conversations.

If any part of this study takes place at Children's Hospital of Alabama (TCHA), this consent document will be placed in your file at that facility. The document will become part of your medical record chart.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution.

You may be removed from the study without your consent if the sponsor ends the study, if the study doctor decides it is not in the best interest of your health, or if you are not following the study rules.

If you choose to withdraw from this study before you receive any genetic information:

- No genetic information from this study will be reported to you. If it has not yet been reported to your child's doctor, we will not do so.
- Your blood sample will be destroyed and no new genetic information will be generated or reported to you or your child's doctor.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- If the analysis of your DNA has been completed, this information will be retained for the study.

If you withdraw after you receive genetic information about you and your child:

- Your blood sample will be destroyed and no new genetic information will be generated or reported to you or your child's doctor.
- You will not be contacted to provide new information, additional samples, or participate in additional studies related to this project.
- Your genetic information will be retained as part of the study (see below for details regarding treatment of your information).

If you want to withdraw, please contact Dr. Martina Bebin at 256-533-0833 and write a letter to the following address indicating that you wish to withdraw:

Martina Bebin, MD
North Alabama Children's Specialists
502 Governor's Drive
Huntsville, AL 35801

Cost of Participation

All lab tests, exams, and medical care related to this study will be provided to you at no cost during the 12-month study period. However, you and/or your insurance will need to pay for all other tests and procedures normally offered as part of clinical care, including co-payments, deductibles, and any other financial obligations. This includes any follow-up procedures related to the genetic results that may be recommended by your child's doctor, genetic counselor, or any healthcare provider. This type of follow-up medical testing will be considered part of your clinical care, and will not be paid for by the research study.

Payment for Participation in Research

Each parent that turns in the post-results questionnaire at the end of the study will be compensated \$10 by check within one month. If we ask you to return for an interview, and you complete the interview, you will receive \$100 check within one month as compensation for your time and effort. No other compensation will be offered. Each parent that participates will receive compensation.

Payment for Research-Related Injuries

UAB, HudsonAlpha, and NIH have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Significant New Findings

You will be told by your doctor or the study staff if new information becomes available and might affect your choice to stay in the study.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact Dr. Martina Bebin. She will be glad to answer any of your questions. Dr. Bebin's number is 256-533-0833.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Storage of Specimens for Future Use

We will keep your blood sample and the sample of your child for confirmation of results and future research relevant to this research. If you do not want your blood sample or your child's blood sample to be used for future research, you should not take part in this study.

Please initial your choice below:

I agree to allow my samples to be kept and used for future genetics research on developmental delays.

I do not agree to allow my samples to be kept and used for future genetics research on developmental delays.

It is possible that, as our knowledge of human genes and genetics improves, the interpretation of the clinical relevance of your genetic information may change in the future. However, we do NOT promise to provide you with updates or revisions to your genetic results after your results are disclosed to you as part of this research study.

Your Medical and Genetic Information: the medical record

Your participation in this study and the results of your genetic testing will be documented in our research records, but NOT in the permanent medical record for you or your child. If you decide to seek additional health care based on the results of the genetic testing, we can, at your request, add specific test results to the permanent medical record.

To aid in your decision-making, it is important to know about a Federal law, called the Genetic Information Nondiscrimination Act (GINA). The GINA makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. If you decide to include genetic information in your permanent medical record, this law protects you in the following ways:

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law. However, this Federal law doesn't protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Members of the United States military may not have the same protections under this law. More information about GINA can be found at www.ginahelp.org or you can ask a member of the research team to give you additional details about GINA.

More about your Medical and Genetic Information: research results

We consider the privacy of your information to be a high priority and will take a variety of steps to ensure that privacy. However, it is important for researchers to share some of the information that they get from studying human samples. We will never share personally identifiable information, like names and addresses, with anyone outside of this research study. However, parts of your information may be shared.

Some of your genetic information, limited to very small subsets that would not pose privacy loss risks to you, may be published in scientific journals or other public venues to facilitate sharing of the knowledge that may be learned by analyzing your DNA and DNA from other individuals.

We may share anonymized lists of the DNA differences that we identify in public genetic databases. These databases gather genetic information from large groups of people and are pooled together such that no specific participants can be identified.

There is a very small chance that some commercial value may result from the use of your donated sample or genetic information. If that happens, you will not receive a share in any profits.

There is one aspect of data sharing from which you may opt out. Unless you specify otherwise, we may place some of your genetic and health information into the national scientific database known as dbGaP (see <http://www.ncbi.nlm.nih.gov/gap>). dbGaP is a database set up by the National Institutes of Health that includes health and genetic information from many thousands of people. Access to dbGaP is available only to qualified researchers at qualified institutions that agree to a variety of privacy-guarding safeguards. Researchers given access to this information have both a legal and ethical duty to protect your privacy and to keep your information confidential. However, because your genetic information is unique to you, there is a small chance that someone could trace it back to you. The risk of this happening is very small, but may grow in the future. Please tell the research staff if you do not want your information to be placed into dbGap.

Please initial your choice below:

- I agree to allow my data to be shared with dbGaP.
 I do not agree to allow my data to be shared with dbGaP.

Contact for Future Research

As new research opportunities are identified, the researchers may wish to perform additional tests on fresh samples or invite eligible participants to enroll in new studies. However, this is not a requirement to participate in this study. A separate consent will be obtained if you wish to participate in future research.

Please initial your choice below:

- You have permission to contact me about new research opportunities that may interest me.
 You do not have permission to contact me about new research opportunities.

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Signatures

You will receive a copy of this signed document. You are making a decision whether or not to participate in this study and/or to have your child participate in this study. Your signature indicates that you have read (or been read) the information provided above and decided to participate and/or allow your child to participate.

Parent(s) Participant Signature Section

Name of Parent Participant

Signature of Parent Participant

Date

Name of Additional Parent Participant (if available)

Signature of Additional Parent Participant (if available)

Date

Signature of Person Obtaining Consent

Date

Signature of Witness

Date

Child Participant Signature Section

Name of Child Participant

Signature of Participant 14-18 Years of Age

Date

Signature of Parent or Guardian

Date

Signature of Additional Parent or Guardian (if available)

Date

Signature of Person Obtaining Consent

Date

Signature of Witness

Date

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____ Maturity _____ Psychological state of the child _____

Signature of Parent or Guardian

Date

Signature of Additional Parent or Guardian (if available)

Date

Signature of Person Obtaining Consent

Date

Signature of Witness

Date

University of Alabama at Birmingham
**AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION
FOR RESEARCH**

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant Name: _____

UAB IRB Protocol Number: X130201001

Research Protocol: Genomic Diagnosis in Children
with Developmental Delay

Principal Investigator: Martina Bebin, MD, FACP

Sponsor: National Human Genome Research Institute of the
National Institutes of Health (NIH)/ HudsonAlpha Institute
for Biotechnology (HudsonAlpha)

What health information do the researchers want to use? All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Principal Investigator, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____

Date: _____

or participant's legally authorized representative: _____

Date: _____

Printed Name of participant's representative: _____

Relationship to the participant: _____