

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH PROTOCOL

Protocol #: 09202 Name of Subject: _____ Project #: _____

2009-08 A Version for affected individuals

Molecular Genetic Studies of Brain Malformations

including

- De novo copy number variation and gene discovery in human brain malformations**
- The role of ARX in normal and abnormal brain development**
- Lissencephaly: the molecular basis of neuronal migration**
- The genetic basis of mid-hindbrain malformations**
- Genomic imbalances in autism**

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You are (your child is) being asked to participate in a research study. A member of the research team will explain what is involved in this study and how it will affect you. This consent form describes the study procedures, the risks and benefits of participation, as well as how your confidentiality will be maintained. Please take your time to ask questions and feel comfortable making a decision whether to participate or not. This process is called informed consent. If you decide to participate in this study, you will be asked to sign this form. Appendix 1 includes a list of all associated research projects.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn about the causes and consequences of many different birth defects of the brain and conditions related to them (Table). This research is being done because many types of birth defects are difficult to recognize, their cause are often not known, and the information that we can give affected individuals and their families is often limited.

Table. Partial list of malformations and related developmental disorders under study

<i>Forebrain malformations</i>	<i>Malformations of Cortical Development</i>	
Agenesis of the corpus callosum	Microcephaly	Lissencephaly (pachygyria)
<i>Mid-hindbrain malformations</i>	Megalencephaly	Subcortical band heterotopia
Cerebellar hypoplasia	Heterotopia	Walker-Warburg syndrome
Dandy-Walker malformation	Polymicrogyria	Muscle-eye-brain disease
Joubert syndrome and related	Schizencephaly	Focal cortical dysplasia
<i>Other birth defects</i>	<i>Neurodevelopmental disorders</i>	
Facial and eye anomalies	Mental retardation	Early childhood epilepsy
Heart, kidney, limb defects	Autism	Early childhood dyskinesias

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 150 individuals take part in this study at The University of Chicago and ~700 throughout the world each year. This includes affected individuals as well as many of their other unaffected relatives.

WHAT IS INVOLVED IN THE STUDY?

During this study, Dr. Dobyns and his research team will collect information about you (your child) for research purposes. A clinic visit with Dr. Dobyns is not required to participate in this study. We will

ask for your contact information and for detailed information from your (child's) medical records that will include medical history and exams, and results of medical tests such as MRI and other imaging studies, routine diagnostic tests and genetic diagnostic tests. We may also request clinical photographs. This information is needed to confirm and correctly classify your (child's) condition. We will also keep any new results generated as part of this research project. This information, including personal identifying information, may be shared with other researchers performing key parts of this research project. The names and contact information for these researchers are listed in the Appendix. This information may also be shared with The University of Chicago Institutional Review Board and representatives of government agencies as required by law to protect the health and safety of human subjects.

This study involves genetic testing. We will use your (child's) blood or other tissue samples to do tests on your (child's) genes. Genes are the material that is passed from parents to children that determine the make-up of the body. The results of these tests will be shared with you whenever they provide clinically useful information. The doctors directing this study will receive the results of these tests and will use this information for the purposes of this research study.

We request 5-7 ml (1 to 1.5 tsp) of blood from adults, 3-5 ml (1/2 to 1 tsp) of blood from children, and less from small infants depending on their weight. We may ask for a second sample if the first sample fails, and may request other samples such as a saliva sample, a skin biopsy or tissue obtained at surgery or autopsy when obtained for regular care. The blood will be used to prepare chromosomes and DNA, the material that contains the genetic code, and may be used to culture living cells. These samples will also be stored for use in future research studies.

WHAT ARE THE RISKS OF THE STUDY?

The risks of this study are uncommon and none are serious. Pain and bruising may occur from having blood drawn (venipuncture), and an infection may occur. Care will be taken to minimize these complications. Rarely, genetic analysis reveals unexpected results, such as discovery of a genetic abnormality unrelated to your (child's) birth defect or the discovery that the man said to be the father of a child is not the true biological father. Should we find unexpected information while analyzing your (child's) sample, we will NOT disclose it to you or others unless we determine that the information would be important for medical management or counseling, such as changing the genetic risk. If this happens, we will first discuss the information with your referring physician or genetic counselor. Should you choose to use information gained from this study in planning a pregnancy, an affected child could be born when this was not expected.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may be direct medical benefit to you (your child). The information gained from the study may help you understand the cause of your (child's) birth defect. While every effort is made to be accurate, our knowledge of the causes of birth defects of the brain is not complete. If our analysis detects a genetic abnormality in your (child's) sample, this information will be provided to you. Due to the complex nature of the information, it must be presented to you by a genetic counselor or physician as part of your (child's) clinical care to make sure that you understand the information correctly and have an opportunity to ask any questions that you may have. We also expect that the information gained from this study will benefit other individuals in the future and medical science generally.

___ You do not have to learn the results of any testing. If you would like to participate in this study, but do NOT want to know the results of the analysis of your (child's) sample, please sign your initials here.

HOW LONG WILL I BE IN THE STUDY?

We think that you will be in the study indefinitely, as new research testing is likely to continue for many years and may provide useful information for medical science and for you personally. We may ask for updated clinical information periodically. If you want your (child's) sample to be withdrawn from analysis at any time, please contact us, and the sample will be discarded.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you may arrange for evaluation by a specialist, usually a Clinical Geneticist or Pediatric Neurologist, at most large medical centers. Alternatively, you may schedule a clinic visit with Dr. Dobyns without participating in research. The decision whether or not you wish to participate in this study will not affect your care at The University of Chicago Hospitals.

WHAT ARE THE COSTS?

Genetic testing performed on a research basis is done at no cost for the individual with a brain malformation and for his or her parents. Neither you nor your insurance (or national health care program) will be billed for any studies that are considered experimental in nature. Once a genetic change has been found in you (your child), we will test your (child's) parents at no charge, but samples from other relatives and prenatal testing are tested on a fee-for-service basis. Another charge you may receive is the small cost of having your (child's) blood drawn and mailed. We can reimburse you for this cost, once you have provided us with a receipt. This research project is not a clinical DNA bank. We will maintain samples 5-10 years or longer, but cannot guarantee that samples will be available in the future due to the possibility of storage failure or use of all of the available sample for research tests.

Clinical evaluations performed by Dr. Dobyns or another member of the research team, and genetic counseling needed to explain research results to you are not part of this study. Thus, you or your third party payer (your insurance company or Medicare in the U.S.A.) must be responsible for payment of charges for appointments or tests that are considered part of standard clinical care for children with a brain malformation or other developmental disorder. This does not apply to you if you live in a country with a national health insurance program, such as Canada, as the health system covers these services.

If you suffer an unanticipated injury as a direct result of this research and require emergency medical treatment, the University of Chicago Medical Center will provide such treatment at the University of Chicago Medical Center at no cost to you. Costs of related non-emergency care for an unanticipated research injury will be covered if that care is provided at the University of Chicago Medical Center. You must notify Dr. Dobyns as promptly as possible after your injury in order to receive this care. An injury is "unanticipated" if it is not one of the known effects of a study drug, medical device or procedure, and is not the result of your disease or condition. If you think that you have suffered a research related injury, you must let Dr. Dobyns know right away.

WILL I BE PAID FOR MY PARTICIPATION?

No payment will be made for your (child's) participation in this study.

WHAT ABOUT CONFIDENTIALITY?

Study records that identify you will be kept confidential. We will assign a roster number for each participant and separate accession numbers for each sample received in the laboratory. Data linking each code to your (child's) name or other identifying information will be kept confidential. For the duration of your participation, your (child's) private health information will be stored in Dr. Dobyns' and Dr. Das' office suites as electronic files, paper files or both. All research samples will be stored in Dr. Dobyns' or Dr. Das' laboratories. Paper files will be kept in locked file cabinets, with the office suite locked whenever study personnel are not present. Electronic data will be kept in password protected databases and as miscellaneous electronic files on computers housed within Dr. Dobyns' or Dr. Das' locked office suite or laboratory. These are backed up on servers or CD disks. Computers connected to a network are protected by a firewall maintained by The University of Chicago. Only study personnel

working with Drs. Dobyns, Das or Millen will have access to these data. When paper is discarded, it will be shredded or burned. When samples are discarded, they will be stripped of identifying marks. If we want to use your (child's) stored sample for any unrelated research project, we will contact you to give or withhold separate consent.

The data collected in this study will be used for the purpose described in the form. By signing this form, you are allowing the research team access to your (child's) medical records, which include Protected Health Information (PHI). This consists of any health information that is collected about you (your child), which could include your (child's) medical history and new information collected as a result of this study. The research team includes the individuals listed on this consent form and other personnel involved in this study at The University of Chicago. This consent form document will be kept by the research team for at least 6 years.

As part of this study, Dr. Dobyns and his research team may share private health information such as medical records, brain imaging studies, test results and photographs with collaborating researchers who are listed in Appendix 2. This information is being sent as these researchers may provide further expert opinions regarding your (child's) diagnosis and classification, perform additional research testing relevant to your (child's) condition, or assist in analyzing data regarding your (child's) results. The study sponsor or their representatives, including monitoring agencies, may also review your medical record. Please note that these individuals may share your health information with someone else. If they do, the same laws that The University of Chicago must obey may not protect your health information. Your records may be reviewed by federal agencies whose responsibility is to protect human subjects in research including the Food and Drug Administration (FDA) and Office of Human Research Protections (OHRP). In addition, representatives of The University of Chicago, including the Institutional Review Board, a committee that oversees research at The University of Chicago, may also view the records of the research. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

We will provide a brief summary of Dr. Dobyns' analysis of clinical data to the referring physician or genetic counselor on request, and to other physicians or genetic counselors at your request. However, this is not a clinical service, and participation in this study is not a substitute for a clinical evaluation by a qualified specialist. When clinically relevant, the results of genetic tests will be confirmed in a clinical (usually Dr. Das') laboratory and this result may become part of your (child's) medical record. During your participation in this study, you will have access to your (child's) medical record. Dr. Dobyns is not required to release research information that is not part of your medical record. The study results will be kept in your research record and may be used by the research team indefinitely, and any research information in your medical record will be kept indefinitely. Information from this study may be used in medical publications or presentations. Your (child's) name and other identifying information will be removed before this data is used. If we wish to use identifying information in any publications, we will ask for your approval at that time.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. If you choose not to participate in this study, your care at The University of Chicago/University of Chicago Hospitals will not be affected. You may choose not to participate at any time during the study. Leaving the study will not affect your care at The University of Chicago or University of Chicago Hospitals. If you choose to no longer be in the study and you do not want any of your future health information to be used, you must inform Dr. Dobyns in writing at the address on the first page. Dr. Dobyns may still use your information that was collected prior to your written notice. We will tell you about significant new information that may affect your willingness to stay in this study. Please note that this consent form document does not have an expiration date. Also, you will be given a signed copy of this document.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

You have talked to Dr. Dobyns or another member of the research team, and had the opportunity to ask questions concerning any and all aspects of the research. If you have further questions about the study, you may call Dr. Dobyns at 773-834-3597 (U.S.A phone code). Your own physician or genetic counselor will often be familiar with the study and able to assist with questions. If you have a research related injury, you should immediately contact the Geneticist on call at The University of Chicago Hospitals by contacting the page operator at 773-153-1880. If you have questions concerning your rights in this research study you may contact the Institutional Review Board, which is concerned with the protection of subjects in research projects. You may reach the Committee office between 8:30 am and 5:00 pm, Monday through Friday, by calling (773) 702-6505 or by writing: Institutional Review Board, The University of Chicago, McGiffert Hall, 5751 S. Woodlawn Avenue, 2nd Floor, Chicago, IL, 60637.

CONSENT**Subject**

The research project and associated procedures have been explained to me. The experimental procedures have been identified and no guarantee has been given about the possible results. I will receive a signed copy of this consent form for my records. I agree to participate in this study. My participation is voluntary and I do not have to sign this form if I do not want to be part of this research study.

Signature of Subject: _____

Date: _____ Time: _____ AM/PM (circle)

Child or Handicapped Subject's Assent

While it is not always possible for a young child to fully consent to a research study, some children can and should have the study explained to them and consent to having a blood sample drawn. Please check initial one of the following statements:

___ Our child/dependent is too young or too intellectually impaired to comprehend an explanation of this study. As his/her parents/guardians, I/we permit his/her participation in this study.

___ The information in this consent has been described to our child/dependent in a language he/she can understand. Our child/dependent willingly assents to participate in this study, as indicated below.

Parent/Guardian or Legally Authorized Representative

I give my permission for my child/relative to participate in the above described research project.

Signature of Parent/Guardian or
legally authorized representative: _____

Date: _____ Time: _____ AM/PM (circle)

For Minor / Dependent Study Participants

You are being to ask to be in the research study that has been explained to you. To be in the study, you have to have some blood drawn. You do not have to be in the study if you do not want to. If you want to, and you understand what you have been told about the study, please sign below.

Assent of study participant: _____

Person Obtaining Consent

I have explained to _____ the nature and purpose of the study and the risks involved. I have answered and will answer all questions to the best of my ability. I will give a signed copy of the consent form to the subject and family.

Signature of Person Obtaining
Consent: _____

Date: _____ Time: _____ AM/PM (circle)

Investigator/Physician

Signature of
Investigator/Physician: _____

Date: _____ Time: _____ AM/PM (circle)

Appendix 1. Other associated research projects incorporated in this study

<p>Human epilepsy genetics: neuronal migration disorder Molecular characterization of Joubert syndrome Mouse models of 6p25 Dandy-Walker malformation The genetic link between autism and structural cerebellar malformations Contribution of 22q13 deletion to cerebellar malformations</p>
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Appendix 2. Contact information for other researchers

<p>Joseph G. Gleeson, M.D. University of California, San Diego Department of Neuroscience 9500 Gilman Drive, LBR 482 La Jolla, CA 92093-0665</p>	<p>Joseph Gleeson 858-822-3535 jogleeson@ucsd.edu Dominika Swistun 858-822-3786 dzablock@ucsd.edu</p>
<p>Jeffrey A. Golden, M.D. The Children's Hospital of Philadelphia Abramson Research Center, Rm. 516H 3615 Civic Center Boulevard Philadelphia, PA. 19104</p>	<p>Jeffrey Golden 215-590-4307 goldenj@mail.med.upenn.edu Susan Marone 215-530-3313 marone@email.chop.edu</p>
<p>Renzo Guerrini, M.D. A. Meyer Children's Hospital University of Florence Viale Pieraccini 24 50139 Firenze, ITALY</p>	<p>Renzo Guerrini 39-055-566-2573 r.guerrini@meyer.it Carla Marini 39-055-566-2573 c.marini@meyer.it Elena Parrini 39-055-566-2844 e.parrini@meyer.it</p>
<p>M. Elizabeth Ross, M.D., Ph.D. Weill Medical College of Cornell University 525 East 68th Street, W605 New York, NY 10021</p>	<p>M. Elizabeth Ross 212-746-5550 mer2005@med.cornell.edu</p>
<p>Elliott Sherr, M.D., Ph.D. University of California, San Francisco Department of Neurology 505 Parnassus Avenue, Box 0114 San Francisco, CA 94143-0114</p>	<p>Elliott Sherr 415-502-8039 sherre@neuropeds.ucsf.edu Zoe Strominger 415-502-8039 stromingerz@neuropeds.ucsf.edu</p>
<p>A. James Barkovich, M.D. University of California, San Francisco Department of Radiology 505 Parnassus Avenue, Box 0628 San Francisco, CA 94143-0628</p>	<p>A. James Barkovich 415-353-1655 jimb@radiology.ucsf.edu</p>
<p>Christopher A. Walsh, M.D., Ph.D. Children's Hospital Boston 300 Longwood Avenue Walsh Lab, CLS 14070 Boston, MA 02115</p>	<p>Christopher Walsh 617-919-2923 christopher.walsh@childrens.harvard.edu Brenda Barry 617-919-4371 bbarry@bidmc.harvard.edu Jennifer Partlow 617-919-2865 jpartlow@bidmc.harvard.edu</p>