UNIVERSITY OF CALIFORNIA, IRVINE
CONSENT TO ACT AS A HUMAN RESEARCH SUBJECT

Form 2

CLINICAL GENETICS OF CRANIOSYNOSTOSIS

If you are a parent/legally authorized representative consenting on behalf of your child, "you" refers to "your child" throughout this consent form.

You are being asked to participate in a research study. Participation in this study is **completely voluntary**. Please read the information below and ask questions about anything that you do not understand before deciding if you want to participate. The researcher listed below will be available to answer your questions.

RESEARCH TEAM AND SPONSORS

Lead Researcher:
Virginia Kimonis, MD
Chief, Division of Genetics and Metabolism
Professor of Pediatrics
Tel: (714) 456-2942,
24 Hour Telephone: (714) 506-2063 (Pager)
Email:vkimonis@uci.edu

Study Locations:
UCI ICTS
CHOC
UCI Medical Center

Study Sponsor: NIH

NAME OF SUBJECT: _____ DATE _____

PURPOSE OF THE STUDY:

We would like permission to enroll you as a participant in our research study named: **"Clinical Genetics of Craniosynostosis."**

Due to the fact that a child's brain needs room to grow, the bones which make up our skull are not fused at birth. Rather they are separate bony plates connected by soft tissue. As children mature and their brain volume reaches adult size these bony plates fuse and form the adult skull.

In some instances a child may be born with some of these bone plates fused earlier than normal. This phenomena is called, "cranio (head) synostosis (abnormal development of a joint)."

The connections that separate each individual skull bones are called sutures. The early closing of a suture can lead to an abnormally shaped head and pressure inside of the skull. Craniosynostosis is a phenomenon that may be isolated (no other symptoms) or may be part of a syndrome (other body systems are involved). Craniosynostosis can occur in only one family member or can run in families and several family members may be affected. Either way it is likely that a change or a combination of several changes in our genetic code may have caused craniosynostosis to occur.

WHY IS THIS RESEARCH?

This research project is being done to identify and study the genes associated with these very specific face and skull abnormalities. We would like to determine how variations in our genes relate to the development of craniosynostosis. No other genetic testing will be done without your specific approval. Because face and skull abnormalities have associated medical problems, this study may help us find better methods of diagnosis, treatment and/or prevention of this birth problem.

Participation in this study may require approximately 2 hours of your time.

SUBJECTS:

The expected enrollment at UCI is approximately 100 patients and their parents over a 3-year period. This study is part of a larger research study being coordinated by the University of California at Davis, called the International Craniosynostosis Consortium. It is anticipated that a total of 750 participants will take part in this multi-site study.

Families with at least one child with the presence of a confirmed finding of a skull and/or face abnormality found at birth or craniosynostosis by a clinical geneticist, radiologist, and surgeon will be asked to participate in the study.

The majority of craniosynostosis patients are diagnosed in the first year of life, and therefore, most research participants are expected to be younger than 12 months of age. You can, however, participate at any age.

Study participants will be identified through the pediatric, genetics and craniofacial clinics and support organizations throughout Orange County. Where possible other local hospitals and physicians will be made aware of this research study at UC Irvine, and they might also refer potential participants.

Children over the age of 7 years, who are able to understand the risks and benefits of the study, will be asked to provide their written assent (a simplified version of the form you are signing). If your child is willing to participate in the study, your written consent and your child's assent will

be obtained by the Principal Investigator, Dr. Virginia Kimonis, at the UCI Institute for Clinical & Translational Science (ICTS) or the UCI Medical Center.

PROCEDURES:

Below, we have listed the procedures we would like for you to participate in today. We will explain the procedures in detail to you including who will perform the procedure, the risks and or discomforts involved and the time it takes to perform the procedure. By initialing and checking off on a procedure you are indicating that you understand the procedure and that you are agreeing for the procedure to be performed:

Check /Initials

____ ____ Chart review: Data will be analyzed from your medical records.

We may ask to obtain relevant medical records from you or your physician(s). You will be asked to sign a medical record release form so that we may review medical records that are important to our research. Whenever possible, a review of medical records will be completed prior to the study visit to limit the length of the visit. A medical release form and a UCI HIPAA form for research studies will therefore be mailed to you before your appointment. Once we receive the signed forms back from you we can start to obtain medical records.

____ ____ We will also ask you to complete a medical and family history. This will include questions about your medical history involving medical conditions, surgeries, development milestones and current and past medication. We will also ask you questions about yourself, family history, other children, siblings, grandparents and possibly other family members and ask for a history of other birth defects. These questions may include age, ethnic background, pregnancy history, and exposure to drugs, alcohol, and smoking. Identifying information like names will only be collected on consented individuals. The information obtained will be entered and kept in a password protected database at UCI and paper files will be kept in locked file cabinets.

____ _____ Release of previously collected sample (i.e. blood, cell line, DNA, biopsy tissue etc.) Sometimes your medical provider may have stored previously collected biological samples from you. This could be frozen blood, cells from your blood or your skin which can be grown in the laboratory and multiplied or tissue which was generated either from a biopsy or another surgical procedure (ie bone shavings from the surgical opening of a suture) By initialing this line you are allowing us to transfer such a sample from your provider for analysis. If a surgical procedure is scheduled to happen in the future, we may contact you for permission to collect potential samples for this research study.

____ ____ Digital photographs: We will take digital photographs of you. You might be identifiable in some of these clinical photographs. We will ask you to sign a separate Photograph Release form for all photography. The digital photographs will be entered and stored digitally on a secure server maintained at UCI. To decline photography will not exclude you from the study.

____ ____ Physical Examination (Takes 20-25 mins): We will perform a detailed physical exam that will include ophthalmologic and neurological assessments as part of routine physical examination. This examination will include measurement of height, weight, head-circumference etc. Pulse rate and body temperature will also be measured.

In addition we will take measurements of your skull and face including head circumference, arm span, upper and lower body segments. The measurements of the head and face will be made with a sliding caliper. The eyes will also be examined. Abnormalities of the trunk will be assessed and extremities will be measured. This will either be performed at the UCI Medical Center or at one of the UCI Institute for Clinical & Translational Science (ICTS) by qualified physicians and nurses. If during the physical exam additional clinical care is necessary, the appropriate referrals will be made. The result of this examination will be recorded in the specifically designed physical examination form and the data will be deposited into a password protected database file.

____ ____ Blood Pressure: Painless application of blood pressure cuff.

____ ____ Collection of a Venous Blood Sample (Takes about 5-15 mins): A sample of your blood will be collected, one time only, by inserting a needle into a vein in your arm. If you are an adult, you will give up to 6 teaspoon (3 10 ml tubes, 30 cc). If you are minor you will give an amount of blood proportional to your age. If you are between 16 and 17 years of age, you will give up to 6 teaspoons (3 10 ml tubes, 30 cc); 10-15 years, up to 3 teaspoons (3 5 ml tubes, 15 cc); 5-10 years, up to 2 teaspoons (2 5 ml tubes, 10 cc); and if you are less than 5 years, you will give up to 1 teaspoon (1 5 ml tube, 5 cc). Your blood will be taken at phlebotomy center such as at the UCI Gottschalk Medical Plaza or the UCI ICTS by qualified personnel.

In the event that you may have a blood test scheduled through your private physician in the near future and if you would like to avoid giving blood at the study visit, you may combine this blood draw with one scheduled in the future. Please let us know and we may be able to accommodate your request.

A portion of your blood will be sent to perform DNA and other molecular tests for craniosynostosis in the laboratory of Dr. Simeon Boyd at UC Davis. The remaining blood will be retained by Dr. Kimonis' laboratory at UC Irvine and

stored as DNA for future research and possible establishment of cell lines either locally or at a national cell repository.

The establishment of cell lines from blood or tissue samples is to help reproduce and make the cultured cells last a long time. This helps research continue without having to keep asking for more samples. White blood cells can be cultured from blood samples.

____ ____ Collection of a buccal swab or saliva sample (Takes less than 5 mins): When a blood sample is not available or you would like to avoid having blood collected from you we can collect a cheek (buccal) swab sample or a saliva sample instead. A specialist will wipe the inside of your cheek with a cotton swab to collect cells or will ask you to spit into a cup. These samples will be used for DNA testing

____ ____ You agree that your biological sample may be shared with other researchers in the future. None of your personally identifying information will be released for any other research study in the future

____ _____ You agree that your blood may be shared with Coriell Cell Repository to establish cell lines. None of your personally identifying information will be released to this repository. The Coriell Cell Repository is a non-profit organization that provides biological specimens to investigators for research and teaching purposes. The repository makes cell lines from blood samples that can grow indefinitely in order to perform future research studies. The repository will provide these samples back to Dr. Kimonis for her research studies to further research in craniosynostosis. De-identified samples sent to the Coriell Cell Repository may be provided to other researchers. As a non-profit organization, the only fees associated with the Coriell Cell Repository are related to the costs of processing and shipping the samples. The samples are not marketed profit.

Taking part in this study is voluntary. You may choose not to participate or if you do join the study and change your mind later, you may stop participating in the study at any time without fear or penalty or loss of benefits or change in the present or future care, of which you are entitled.

RISKS AND DISCOMFORTS:

Risk to the subjects from any of the study procedures will be minimal. The clinical and blood evaluations will use the same techniques as those routinely carried out in clinical practice.

Blood Drawing: Minimal risks associated with a blood draw are minor discomfort, bruising, dizziness or rarely fainting or infection. When possible we will draw blood at the time of a clinically indicated procedure so that you may not need to have blood drawn only for research

purposes. The blood collection will be done using standard infection control procedures and in compliance with good clinical practice.

Cheek swabs and saliva collection: Minimal risks associated with cheek swab include mouth discomfort or irritation.

Transfer of previously collected sample by your physician (cell lines, bone shavings, blood etc) : No risk

Physical Examination: You may feel slightly inconvenienced as the doctor measures your face, but this should not cause any discomfort.

Digital photographs: Minimal risk which includes psychological discomfort. Some individuals might not feel comfortable to have their picture taken. Because you might be identifiable in some of these photographs, there is a possible risk of breach of confidentiality, although all efforts will be made to minimize this.

Breach of Confidentiality: Because personal information about you will be collected, there is the potential risk of breach of confidentiality, although all efforts will be made to minimize this. Your medical records will only be reviewed by Dr Kimonis and qualified members of the study team. Medical information will be coded and identifiable information will not be shared with our collaborators. The results of the tests performed for research purposes will NOT be placed in your medical records. A copy of this consent form will NOT be placed in your medical record.

Genetic Research: There is the risk that we may find that you or a member of your family may have a gene that can cause a congenital abnormality. Some people involved in genetic studies feel anxious about the possibility of carrying an altered gene that places them at risk or that may be passed on to children. If these feelings arise at any time during the study, you may contact us and we will arrange for you to speak with a genetic counselor. There is also a risk that you or a member of your family may have such a gene and we do not detect it in this study.

You should be aware that because we are testing family members we may detect instances of non-paternity or adoption. If you wish, you may let us know in confidence if this is a possibility, since it may otherwise interfere with our analysis. In all cases, this information will be kept in the strictest confidence and will not be divulged to anyone including you.

You should also be aware that there might be social and economic disadvantages, which can be associated with the gathering of genetic information. You should understand that our testing might find an inherited defective gene, which puts you or a relative at risk for a genetic disorder in the future. Genetic information divulged to the wrong source, could affect you and your family if an insurance company or employer acquired this genetic information. A new Federal law, called the Genetic Information nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you

based on your genetic information. We will do our best to keep all information confidential and only with your permission would we make this information available to others.

Research results will not be available to you or your physician. However, there are situations where we may suspect that you have a known genetic syndrome. In such cases, an earlier diagnosis may prevent or alleviate long-term medical complications. In addition, evaluation of other family members may identify individuals at risk for having a child with craniosynostosis syndrome. If the study team obtains information that they think might be significant to your family and if you provided permission for recontact, we will have the results confirmed by a second certified clinical laboratory.

Most laboratories will ask for fresh blood samples in order to ensure accuracy of the results. If important, abnormal results are confirmed, they will be reported to the Principal Investigator and made available to you by Dr Virginia Kimonis or a physician of your choice at no cost to you or your insurer. Genetic counseling will be provided and names of outside resources will be given to you. And since this study may involve patients and his/her parents, information will only be shared with the individual him/herself and parents, unless the family requests otherwise. This information will not be shared with any other family member other than the individual him/herself and parents, unless the family signs a release of medical records. Parents will be given the option not to receive the information about themselves.

You should also be aware that it is possible that we may not detect changes in DNA that might cause craniosynostosis, even if present. Therefore, you should not assume that these changes are absent or that you are not at risk for having another child with craniosynostosis, if we do not notify you of any abnormalities.

If we find a genetic change of potential significance to you, do we have permission to contact you?

_____ Yes _____No

<u>BENEFITS</u>:
There is no direct benefit to you from being in this study. However, we hope that the information obtained may help us in the development of accurate and efficient diagnostic testing and better treatment strategies of people with these conditions.

Benefits for society are potentially great if the scientific and health communities gain information about the syndrome genes, their function as they relate to normal craniofacial development and the pathogenesis of these conditions.

ALTERNATIVES TREATMENTS:
The only alternative is not to participate in this research study. This research study does not involve medical treatment, and will not interfere with any future care you or your family receives at UC Irvine or any referring facility.

COST/COMPENSATION:
It will not cost you anything to be in this study. You will be paid $75 for your participation in the study.

Compensation for Injury
If you are injured as a result of your participation in this study, the University of California will provide you reasonable and necessary medical care to treat the injury at no cost to you or to your insurer/third party payer. The University of California does not routinely provide any other form of compensation for injury. It is important that you report any suspected study-related injury to the research team listed at the top of this form immediately.

WITHDRAWAL FROM THE STUDY:
You are free to withdraw from this study at any time without any obligations or consequences. If you decide to withdraw from this study you should notify your study doctor.

CONFIDENTIALITY:
Your research records will be stored in a very restricted-access area.

Subject Identifiable Data
All identifiable information that will be collected about you will be removed from biological samples and replaced with a code. In order to protect your privacy, a list linking the code and your identifiable information will be kept separate from the research data. Dr. Kimonis and qualified research personnel will be able to de-code these records and identify you. Identifiable information will not be shared with our collaborators. Medical exam forms will include your name and date of birth. These Forms will be kept in locked file cabinets and will not be included in your medical chart. All study data and consent forms will be kept in a separate locked file cabinet and will be accessible only to the principal investigator and qualified research personnel at UCI.

Data from this study also may be used in medical publications or presentations. Your name and other identifiable information will be removed before the data is used. If we wish to use identifying information in publications or presentations (i.e., facial photographs), the research team will ask for your approval at that time.

Data Access
The research team, authorized UCI personnel and regulatory entities such as the Office of Human Research Protections (OHRP), may have access to your study records to protect your safety and welfare. Any information derived from this research project that personally identifies you will not be voluntarily released or disclosed by these entities without your separate consent, except as specifically required by law. Research records provided to authorized, non-UCI entities will not contain identifiable information about you. Publications and/or presentations that result from this study will not include identifiable information about you.

Data Storage
Storage of paper files and electronic data:
All paper files such as medical records will be maintained in a secure location at UCI. Only authorized individuals will have access to it.
All electronic research data will be stored on a secure network with password protection.

Storage of collected biological Samples:
All collected biological samples will be sent to Dr. Boyd at UC Davis where they will be stored and analyzed. Dr. Boyd will also prepare cell lines from blood obtained. These cell lines will also be stored in Dr. Boyd's laboratory. All samples will be stripped of personal identifiers (names) and replaced with a code and only Dr. Kimonis will have a key to the code. With your consent, blood samples will be sent to Coriell repository, Camden, NJ to establish cell lines that can be kept growing indefinitely. All identifiable information that will be collected about you will be removed from the sample and replaced with a code

Data Retention
Due to the fact that this study involves children, all study records will be retained for seven years after all minors are enrolled in the study reach the age of 18 years The researchers also intend to keep the de-identified biological samples in a repository indefinitely. Other researchers will have access to the samples for future research but no information that can identify you will be released with the samples.

OTHER CONSIDERATIONS:
Use of Specimens
Any specimens (e.g., tissue, blood) obtained for the purposes of this study will become the property of the University of California, Irvine (UCI). Once you provide the specimens you will not have access to them. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

With your consent, as noted above, blood will be sent to the Coriell Cell Repository in Camden, NJ, to establish cell lines that can be kept growing indefinitely. All identifiable information that

will be collected about you will be removed from the sample and replaced with a code. The Coriell Cell Repository is a non-profit organization, which may sell your de-identified sample to other scientists in research and teaching. The fees charged to other researchers are to cover costs of the processing, storage and shipping of the samples. These samples are not being marketed for profit. Researchers who purchase these samples must sign an Assurance Form that states they will use them for research only and not commercialize them in any way.

Investigator Financial Conflict of Interest
No one on the study team has a disclosable financial interest related to this research project.

NEW FINDINGS:
If, during the course of this study, significant new information becomes available that may relate to your willingness to continue to participate, this information will be provided to you by the investigator.

IF YOU HAVE QUESTIONS:
If you have any questions about this study, your participation or an emergency situation occurs you should contact the principal investigator listed at the top of this consent form.

If you are unable to reach a member of the research team listed at the top of the form and have general questions, or you have concerns or complaints about the research study, research team, or questions about your rights as a research subject, please contact UCI's Office of Research by phone, (949) 824-6068 or (949) 824-2125, by e-mail at IRB@rgs.uci.edu or in person at 5171 California Avenue, Suite 150, Irvine, CA 92697-7600..

VOLUNTARY PARTICIPATION:

You should not sign this form unless you have read the attached "Experimental Subject's Bill of Rights" and have been given a copy of it and this consent form to keep. **Participation in this study is voluntary.** You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled.
Your decision will not affect your future relationship with UCI or quality of care at UCI Medical Center. Your signature below indicates that you have read the information in this consent form and have had a chance to ask any questions you have about the study.

I agree to participate in the study.

Signature of Subject (ages 16 and older)	DATE
Printed Name of Subject	DATE
Signature of Parent/Legally Authorized Representative	DATE
Printed Name of Parent/Legally Authorized Representative	DATE
Signature of Parent/Legally Authorized Representative	DATE
Printed Name of Parent/Legally Authorized Representative	DATE
Signature of Witness	DATE
Printed Name of Witness	DATE
Signature of Researcher	DATE
Printed Name of Researcher	DATE

UNIVERSITY OF CALIFORNIA, IRVINE
Experimental Subject's Bill of Rights

The rights listed below are the right of every individual asked to participate in a research study. You have the right:

1. To be told about the nature and purpose of the study.
2. To be told about the procedures to be followed in the research study, and whether any of the drugs, devices, or procedures is different from what would be used in standard practice.
3. To receive a description of any side effects, discomforts, or risks that you can reasonably expect to occur during the study.
4. To be told of any benefits that you may reasonably expect from the participation in the study, if applicable.
5. To receive a description of any alternative procedures, drugs, or devices that might be helpful, and their risks and benefits compared to the proposed procedures, drugs or devices.
6. To be told of what sort of medical treatment, if any, will be available if any complications should arise.
7. To be given a chance to ask any questions concerning the research study both before agreeing to participate and at any time during the course of the study.
8. To refuse to participate in the research study. Participation is voluntary. You may refuse to answer any question or discontinue your involvement at any time without penalty or loss of benefits to which you might otherwise be entitled. Your decision will not affect your right to receive the care you would receive if you were not in the experiment.
9. To receive a copy of the signed and dated written consent form and a copy of this form.
10. To be given the opportunity to freely decide whether or not to consent to the research study without any force, coercion, or undue influence.

If you have any concerns or questions regarding the research study you should contact the research team listed at the top of the consent form.

If you are unable to reach a member of the research team and have general questions, or you have concerns or complaints about the research study, research team, or questions about your rights as a research subject, please contact the UCI's Human Research Protections Program in the Office of Research by calling (949) 824-6068 or (949) 824-2125 Monday – Friday, 8 am – 5 pm; or by e-mail at IRB@rgs.uci.edu; or by writing us at 5171 California Avenue, Suite 150, Irvine, CA 92697-7600.