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Cure and Prevention of Birth Defects

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11 August 2006

Dear Colleagues,

Thank you for your interest in the mutational screening of nephronophthisis patients.

We are performing deletional analysis in the *NPH1* gene (nephrocystin) and may perform mutational analysis in other genes known to cause nephronophthisis (NPH) if the clinical situation strongly suggests it. Samples are kept indefinitely and may be used to identify new genes which cause NPH, or examined for mutations in new genes found to cause NPH, as this information becomes available. This genetic analysis is investigational and is performed in the setting of a research laboratory and there are no universal standards for the performance of these studies. The investigators endeavor to attain the highest standards in their analysis, but this analysis should not be considered a diagnostic test; rather, an investigational genetic test not intended to replace other clinical or laboratory evaluations or treatments that would otherwise be considered the standard of care.

As these genetic tests are presently considered investigational, and a part of a research protocol. There is no cost for the blood draw, shipping, or processing of the samples to the patients, or family members of the patients, who agree to participate in the study. Office visits to physicians or genetic counselors are not paid for by this study, nor are any other laboratory tests. Results of genetic analysis are generally available 4-6 months following the receipt of a sample. At this time we will report the presence or absence of a deletion in the *NPH1* gene. If no deletion is present these results will not provide a definitive diagnosis for the cause of this individual's disease. We will continue to perform mutational analysis on these samples, but results defining the genetic mutation responsible for a particular patient's disease are likely to take a much longer time (*eg.* months to years), and in some cases a genetic cause for disease may never be found. All results are transmitted directly to the corresponding physician and not to individual participants. Participants will therefore need to depend upon their local physician to communicate and explain the results of the genetic tests. The investigators would be happy to discuss the results of the genetic testing with any local physician who wishes to do so. **No results will be reported for individual participants who do not have evidence of kidney disease at the time of enrollment.** If an individual develops evidence of kidney disease after enrolling in the study, a local physician may contact the investigators at which time results of any genetic testing, which has been performed, can then be released to the local physician. Local physicians or their representatives are expected to review the consent document with prospective participants indicating that they feel the participant understands the nature of the study by signing the consent document before the participant signs the consent document. In addition to the copy that is returned to the investigators, the participant and the local physician should also keep a signed copy of the consent.

Please return the following items to the investigators:

1. Signed consent document
2. Health questionnaire
3. Blood sample: 3-10 ml EDTA or Na-Heparin blood for each participant

Blood samples without a signed consent document cannot be processed or analyzed.

If you like, you can use one of our personal courier accounts. For information on the account numbers, please contact Susan Allen at sjallen@umich.edu or Juliana Helou at jhelou@umich.edu.

Please e-mail us at the time of shipping with the shipping number, so that we can track the package and ensure safe delivery. Thank you again for your participation. Please do not hesitate to contact us with any questions or concerns.

Best Regards,

A handwritten signature in blue ink, appearing to read "F. Hildebrandt". The signature is written in a cursive style with a large initial "F" and a stylized "Hildebrandt".

Friedhelm Hildebrandt, M.D.

Professor of Pediatrics and of Human Genetics
Frederick G. L. Huetwell Professor for Cure and Prevention of Birth Defects

BLOOD SAMPLE COLLECTION FOR MUTATIONAL ANALYSIS

Instructions for blood collection and shipping:

1. Review and sign consent document with each patient from whom blood is to be drawn.
2. A single 3-10 ml EDTA or Na-Heparin tube of blood is required from each individual. Use sterile technique to obtain blood sample. Invert several times after drawing to prevent coagulation. **Always store blood at room temperature -- do not freeze.**
3. Use FedEx for the shipment of blood.
Please indicate contents as blood or DNA, non-hazardous, non-toxic, non-infectious.
Value \$1.00
4. When returning blood sample please include:
 - a. Blood sample
 - b. Signed consent documents
 - c. Health questionnaire
 - d. Any available renal imaging or biopsy reports
5. Please return these items to the following address:

The shipping address is:

Dr. F. Hildebrandt
University of Michigan
Department of Pediatrics
8240 MSRB III
1150 West Medical Center Drive
Ann Arbor, Michigan 48109-0646, USA

6. Once you are ready to ship samples, please let us know the shipping number so we can track the package and ensure its safe delivery. Please email the shipping number to: sjallen@umich.edu or jhelou@umich.edu
7. Results for NPHP1 deletion analysis are generally available in 4-6 months and a report will be sent to you when they are available.

Thank you for your interest. Please do not hesitate to contact us with any questions or concerns.

Juvenile Nephronophthisis (Questionnaire)

Prof. F. Hildebrandt, M.D.

Thank you very much for taking the time to fill out this form.

General Patient Information

Last name: _____ First name: _____ DOB: ___(mm)/___(dd)/___(yy)

m f

height: _____ cm

weight before illness: _____ kg

consanguineous parents

yes no

relatives with renal diseases

mother

sister

father

others: _____

brother

I. Initial Clinical Examination: ___(mm)/___(dd)/___(yy)

1. Symptoms (initial)

acute event

oedema

during regular examination

high blood pressure

polyuria

need of treatment

polydypsia

others:

2. Laboratory findings (initial)

Blood studies:

hemoglobine _____ g/l

HCO₃ _____ mEq/l

hematocrit _____ %

GFR _____ ml/min

Na _____ mmol/l

creatinine _____ mg/dl

K _____ mmol/l

serum protein _____ g/l

Ca _____ mg

albumin _____ g/l

P _____ mg

immunologic abnormalities

SGOT _____ IU

(immunoglobulins/

SGPT _____ IU

complement components)

pH _____

following: _____

Urine analysis:

urine concentration

_____ mosm/kg H₂O

aminoaciduria

hematuria

proteinuria _____ g/day or

_____ g/g crea

selective

nonselective

3. Imaging techniques

bone age _____

medullary cysts

increased echogenity

ultrasonography

4. Renal biopsy

1st biopsy

2nd biopsy

____/____

____/____

(mm/yy)

(mm/yy)

Nephronophthisis (NPH)

others: _____

Patient Name: _____

II. Treatment

Dialysis / renal transplantation

date of end stage renal failure: ___/___/___
1st transplantation: ___/___/___
2nd transplantation: ___/___/___
(mm/yy)

- unsuccessful transplantation because of:
- recurrence
 - graft loss because of:
 - recurrence
 - rejection

III. Extrarenal Association

The patient suffers / suffered from one of the following diseases:

- | | | |
|---|--|--|
| <input type="checkbox"/> deafness | <input type="checkbox"/> short stature | <input type="checkbox"/> urinary/genital tract anomalies |
| <input type="checkbox"/> blindness/retinitis pigmentosa | <input type="checkbox"/> newborn's tachypnea | <input type="checkbox"/> heart anomalies |
| <input type="checkbox"/> microcephaly | <input type="checkbox"/> hexadactylia | <input type="checkbox"/> allergy |
| <input type="checkbox"/> mental retardation | <input type="checkbox"/> vermisaplasia | <input type="checkbox"/> others: _____ |

IV. Remarks

Thank you very much for your assistance.

Please provide us with the following information in order to facilitate further correspondence

Name: _____ Phone: _____

Address: _____ Fax: _____

_____ E-mail: _____

this study should not replace any cares or treatments that would otherwise be considered the standard of care. Results are only reported for individuals who are determined to have nephronophthisis by their local physician. No results will be reported for participants without a diagnosis of nephronophthisis. Results will only be reported to the local physician and only if approved by the participant. Results cannot be directly reported to participants.

Who is eligible to take part in the study?

Individuals who may have nephronophthisis, as determined by a kidney specialist, and their parents will be eligible, siblings who are affected by nephronophthisis would also be eligible. In cases in which the parents of the affected individual are consanguinous (ie. they share a blood relationship) more distantly related family members may be considered eligible for the study.

*Note: it is **very important** for you to give the researchers **accurate** and **complete** information about your **medical history** and condition.*

How many people (subjects) are expected to take part in the study?

Over 500 families have enrolled in the study over the last ten years. Based upon this experience we would expect to enroll about 1 new family a week.

How long will I be asked to participate in the study - and how long will it take to complete the study?

Enrollment in the study will consist of the review of the consent document with your doctor and a routine venous blood draw. The researchers will then analyze the blood sample for mutations in the known genetic causes of nephronophthisis. These results are generally available in 4-6 months. At this time we will report the presence or absence of a deletion in the *NPHP1* gene. If no deletion is present these results will not provide a definitive diagnosis for the cause of this individual's disease. We will continue to perform mutational analysis on these samples, but results defining the genetic mutation responsible for your particular disease is likely to take a much longer time (eg. months to years) and in some cases a genetic cause for the disease may never be found. Results will be communicated to your doctor at that time if you request it and you are eligible to receive results. Results will only be sent for individuals who already have a diagnosis of nephronophthisis. Family members of affected individuals who do not have evidence of nephronophthisis are not eligible to receive results. The DNA taken from the blood sample will be stored indefinitely for the evaluation of the genetic causes of nephronophthisis exclusively as described in this document.

4. What happens to subjects in this study

What exactly will be done to me and what kinds of investigational procedures or treatments will I receive if I agree to be a research subject?

In order to enroll in this study you must review this document with your doctor, give a blood sample and return a signed copy of this document and a signed copy of a health questionnaire with the blood sample to the investigators. The health questionnaire will contain your age, current laboratory values and imaging studies or biopsy results that you may have had done already as a part of your health care to this point. If you are known to have kidney disease as determined by your doctor, a report of the results of genetic testing for nephronophthisis can be sent to your doctor if you wish. Results cannot be reported directly to participants, but will be returned to each participant's primary physician. No results will be reported for individuals who do not have a diagnosis of kidney disease. All samples received will be saved indefinitely, unless the participant withdraws from the study. This type of research can take years, if you develop kidney disease after enrolling in the study your doctor is encouraged to inform the investigators of this change and you would be eligible to receive results of genetic testing if you desired them.

A portion of the white blood cells obtained from the initial blood draw may be isolated from the blood sample and infected with a virus so they can be grown indefinitely in culture as a source for further DNA or RNA isolations. The DNA or RNA obtained from these isolations will only be used for mutational analysis.

This research project is designed to identify the causes of nephronophthisis. There is currently no treatment for nephronophthisis, and this study does not offer any treatments.

The cost of office visits to local physicians or genetic counsellors are not covered by this study, nor is any testing other than the blood draw for the DNA sample requested by this study.

Will I receive any other information about my participation in the study?

If the researchers develop or learn of significant new findings during the study that may affect your willingness to continue to participate, they will contact your physician. If new information is provided to you after you join the study, you may be asked to sign a new consent document to continue participating. Results can be made available to the local physician of individuals who are felt to have the disease prior to testing. Individuals who have no evidence of kidney disease will not be eligible to receive results. If an individual who was healthy at the time of enrollment and blood collection subsequently develops kidney disease, they are encouraged to contact the investigators. At that time results from any genetic testing which have been done can be made available to their physician.

5. Risks and potential benefits of the study

What risks will I face by participating in the study?

The known or expected risks for people participating in the study include:

The risk for routine venous blood draw which include discomfort, bruising, faintness or lightheadedness and very rarely infection.

The risk for identifying a genetic cause of disease can include difficulty in obtaining insurance or increased cost of insurance. However, since insurance companies do not cover the costs for genetic testing, blood draws for genetic testing or shipping and handling of the blood for genetic testing in this study they are not entitled to the results of this study. The investigators will not disclose any findings of this study to anyone other than the participant's private physician. If desired the researchers will not report any results to the participant's private physician.

The risk for learning of a genetic cause of disease may cause the participant emotional distress which could result in depression or anxiety. We hope to minimize distress caused by this information as we report only for individuals who are already aware that they have kidney disease and therefore, this information will only provide a definitive diagnosis for people who are already known to have kidney disease. Costs for genetic counseling or office visits related to the discussion or review of genetic testing performed in this study may generate costs that are not reimbursed by this study.

As with any research study, though, there may be additional risks of participating that are unforeseeable or hard to predict.

What will be done to reduce or monitor these risks?

The blood draw will be performed in a controlled environment using antiseptic technique. Your insurability will not be jeopardized by the investigators, as no information from this study is shared with anyone other than the participant's private physician if so desired.

Please consider the emotional impact that receiving the results of this study will have for you. Your participation in this study does not require that the results of the study be reported to your physician. If you do not understand potential ramifications of learning the results of this study you are encouraged to discuss these with your local physician, the investigators or obtain genetic counseling prior signing this consent and enrolling in the study. This study does not cover the costs of genetic counseling or physician visits to review or discuss results of this study before or after results become available.

What happens if I am hurt or become sick as a result of the study?

This study has been designed to minimize expected risks to you and other participants. However, as is the case with all medical care, you may experience problems or side effects even when precautions are taken to avoid them. If complications occur, the researchers or University of Michigan will help arrange for medical treatment, including, if necessary, emergency treatment. This study does not, however, pay for these related medical or other costs. Therefore, the costs may be billed to your insurer or you may have to pay for them if your health insurance does not cover them. You do not waive any right to seek additional compensation in the event of a personal injury by signing this form.

*Please note: It is **important** that you tell both the **researchers** and your **regular doctor** about any injuries or side effects you experience while participating in the study.*

Can I expect any benefit for others or myself from participating in the study?

We cannot promise that you personally will receive any benefits from being in this study. However, your participation in this study will help us to move the general understanding of this disease

forward with the hope that effective treatments will be developed in the future.

If I participate in this study, can I also participate in other studies?

Yes

6. Other choices (*alternatives to participating in the study*)

If I decide not to be in this study, what may happen to me or what other choices are there?

We cannot offer genetic testing to those who do not enroll in the study.

7. Ending The Study

If I want to withdraw from the study, what should I do?

You can withdraw from this study at any time without loss of any non-study related benefits to which you would have been entitled before participating in the study. If you want to withdraw, you may do so by notifying the study representative listed in the "Contact Information" section below at the e-mail mutation@renalgenes.org. If you withdraw from the study any existing samples will be destroyed. Existing data will not be destroyed but will be anonymized by removing all personally identifying information such that the data could never be traced back to the participant.

8. Financial Information

Who is sponsoring or funding the study?

- A) National Institutes of Health (NIH)
- B) National Heart Lung and Blood Institute (NHLBI) at Marshfield Medical Research Foundation

Will subjects or their insurers be billed for any costs of the study? If so, which, and what happens if insurance does not cover the costs?

No. If any charges for blood draws, lab tests requested by the investigators or shipping costs are billed to the participant or the participants insurance this is an error and should be brought to the attention of the investigators who will cover these costs.

Are subjects paid or given anything for being in the study?

No

Who has an ownership interest in the study intervention or in the study's sponsors?

The researchers conducting the study:

Friedhelm Hildebrandt, M.D.
Professor of Pediatrics and of Human Genetics
University of Michigan Medical Center
Department of Pediatrics and Communicable Disorders

9. Confidentiality of subject records and authorization to release protected health information

University of Michigan policies and certain federal and state laws require that personal health information be kept confidential but allow disclosures in specific situations. You are not required to sign this document, but if you do not, you will not be able to participate in this study.

Why would my health information be disclosed?

Your health information may be shared with another investigator in collaboration with the investigators of this study. However, if this were to occur no information would be shared which could identify you personally nor will personally identifying information be used in publications or presentations.

What information will be disclosed?

If you agree to participate in this study and sign your name on the last page, you will be giving the University of Michigan, including its Health System (hospitals, health centers, clinics and health care providers) or your local health care provider and other providers involved in your care

permission to disclose your medical information (doctors' notes, lab results, x-rays, hospital charts, biopsy tissues obtained for non-research purposes, etc.) to the researchers. Personally identifying information will be kept confidential by the researchers and will not be shared published or made available to others in any way.

How will the researchers protect my privacy?

Upon receipt of blood samples for DNA analysis, signed consent and baseline health information. All information given a unique code without personal identifiers and is secured in locked cabinets available only to the researchers. DNA samples are labeled with the unique code only, without personal identifiers. When results are shared with other scientists no names or other information which could be used to identify the participant will be shared. No results will be disclosed except at the request of the participant.

Other than the research staff, who might see information about me collected during the study, or other related medical records?

- University of Michigan faculty, staff and contractors responsible for oversight of the research.
- Government officials who oversee research (such as the federal Office for Human Research Protections and the Food and Drug Administration).
- Safety monitoring boards that oversee the safety of this study.
- Research sponsors and their representatives.

When does my permission expire? What happens to information about me after the study is over?

Your permission expires at the end of the study. However, even after the study is complete or after you decide to withdraw from the study, information about you may be used or disclosed as follows:

- To preserve the integrity of the other information collected during the study.
- As part of a data set used for research, educational and other lawful activities that does not include your name, social security number, or other identifying information.
- To University faculty, staff and agents responsible for oversight of the research.
- As required by applicable federal or state law. For example, if you withdraw from the study at any time, a record of your withdrawal and the reasons you gave for withdrawing will be kept as part of the study record. In addition, government officials who are responsible for oversight and review of clinical trials may require certain disclosures.

It is important to understand that once your medical records have been disclosed as described above, they may no longer be protected directly by federal privacy regulations issued under the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"). However, as long as the information is held in any part of the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, please ask your doctor for a copy of the University of Michigan's Notice of Privacy Practices, or visit our website at <http://www.med.umich.edu/hipaa/npp.htm>.

10. Contact Information

For more information about the study or the study procedures or treatments, or to withdraw from the study, contact:

Friedhelm Hildebrandt, M.D.
Professor of Pediatrics and of Human Genetics
University of Michigan Medical Center
Department of Pediatrics and Communicable Disorders
1150 W. Medical Center Drive
Room 8220C, MSRB 3
Ann Arbor, Michigan, 48109-0646 USA
mutation@renalgenes.org

To report any illness or injury you experience during the study, contact the researchers listed above *and your regular doctor*.

For more information about your rights and responsibilities as a research subject, or to express a concern about the study, contact:

University of Michigan Medical School Institutional Review Board (IRBMED)
4673 Kresge I
200 Zina Pitcher Place

Ann Arbor, Michigan 48109-0570
Telephone: 734-763-4768
Fax: 734-763-9603
e-mail: irbmed@umich.edu

Alternatively, you may file an anonymous report by calling the University of Michigan Compliance Help Line at 1-888-296-2481. Privacy violations also may be reported to the Health System Privacy Officer at the same number.

Please provide as much information as possible when you make a report, including the name of the researcher, the IRB Archive number (at the top of this form), and details about the complaint. This will help us do the necessary follow-up.

11. Record of Information provided

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

1. A copy of the informed consent document signed by yourself (the participant) and signed by the person who explained the consent to you and was available to answer your questions.

12. SIGNATURES

Counselling Physician (or Designee):

I have given this research subject information on the study that I believe to a reasonable degree of medical certainty is accurate and sufficient for the subject to understand fully the nature, risks and benefits of the study, and the rights and responsibilities of a research subject. There has been no coercion or undue influence.

Name: _____ Role on Study: _____

Signature: _____ Date of Signature: _____

Option to Receive Results:(please check only one of the following choices):

I may have nephronophthisis and I would like results to be sent to the counselling physician as noted above.

I may have nephronophthisis and I do NOT want results of the genetic testing sent to me or my doctor.

I do not have any evidence of kidney disease at this time and understand that I am not eligible to receive results of this testing.

Research Subject:

I understand the information printed on this form and in the attached materials. I have been given copies of all of these. My questions so far have been answered, I have discussed this study, its risks and potential benefits, and alternatives to participation in the study with:

(Counselling Physician or Designee)

I understand that if I have any additional questions or concerns about the study or my rights as a research subject, I may contact one of the people listed above. I also understand that I will receive a copy of this document at the time I sign it and later upon request. In addition to the copy I receive, copies of this document will be stored in a separate research file.

Signature of Subject: _____ Date: _____

Name (Print legal name): _____

Patient ID: _____ Date of Birth: _____

If applicable: Name, Address, Telephone and Signature of Person Legally Authorized to Give Consent:

Relationship to Subject: Parent Spouse Child Sibling Legal Guardian Other: _____
(please circle one)