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Mutation analysis in nephrotic syndrome and glomerulonephritis, and cloning of new genes for nephrotic syndrome

Dear Colleagues,

Thank you for your interest in the mutational screening of patients with nephrotic syndrome.

We are performing mutational analysis in the *NPHS2*-gene (podocin) and *WT-1*-gene. Our aim is to find out whether there is any correlation between the occurrence of mutations in the *NPHS2*-gene and the clinical outcome of these patients (e.g. response to steroids and cytotoxic drugs, relapse after transplantation) (Karle et al. *J Am Soc Nephrol* 13:388, 2002). 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 these analyses should not be considered diagnostic tests, rather investigational genetic tests, not intended to replace other clinical or laboratory evaluations or treatments that would otherwise be considered the standard of care.

These genetic tests are presently considered investigational and are 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 for physicians or genetic counselors are not paid for by this study, nor are any other laboratory tests. Results of genetic analyses are generally available 3-6 months following the receipt of a sample. 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 a diagnosis of nephrotic syndrome at the time of enrollment.** If an individual develops nephrotic syndrome 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 and indicate 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.

We also kindly ask you to fill out a clinical questionnaire which includes not only important information on the family history, the clinical picture, the response to treatment, and extrarenal associations, but also on the ethnicity of your patient. Recent studies and our own data suggest that ethnic groups are affected differently by mutations in genes causing nephrotic syndrome, such as podocin and nephrin. Our group is interested in elucidating genotype/phenotype correlations in this disease. We, therefore, want to

encourage you to describe your patient's ethnicity in as detailed a way as possible. Please feel free to check more than one box and/or use the "other" checkbox with a more detailed description.

Please return the following items to the investigators:

1. Signed consent document.
2. Health questionnaire.
3. Blood sample: 3-10ml EDTA or Na-Heparin blood for each participant.
4. Outside the U.S.: Customs Invoice (see end of document)

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

As in the past, we are happy to provide free shipping of your blood samples. However, there has been abuse of our customer numbers. Therefore, we would like to kindly ask you to contact our laboratory for information on free shipping. Dr. Gil Chernin will be happy to help you and can be contacted by e-mail at gilc@med.umich.edu. DNA samples can be shipped by regular mail.

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,

Friedhelm Hildebrandt, M.D.

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Idiopathic Nephrotic Syndrome
Questionnaire, version January 25, 2008

Prof. Dr. F. Hildebrandt

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

General Patient Information

Last name: _____ First name: _____ DOB: ____ / ____ / ____
MM DD YYYY

M F Height _____ cm Weight before illness: _____ kg

Consanguineous parents Yes No
 Relatives with nephrotic syndrome Mother Brother
 Father Sister
 Others: _____

Ethnicity: African African American American Indian Arabic Asian Caucasian Central Slavic
 Chinese European Finnish Hispanic Indian Subcontinent Japanese Pacific Islander
 Turkish Other: _____

I. Initial Clinical Examination: ____MM/____DD/____YYYY

1. Symptoms (initial)

- Acute event
- Edema
- During regular examination
- High blood pressure (before steroid therapy)
- need of treatment
- Other: _____

2. Laboratory findings (initial)

Blood studies: Creatine: _____ mg/dl
 GFR: _____ ml/min

Urinalysis: Proteinuria _____ g/day or _____ g/g crea
 selective non-selective

Serum protein: _____ g/l
 Albumin: _____ g/l

Immunologic abnormalities (immunoglobulins / complement components) following:

Hematuria Yes No

3. Renal biopsy

	1 st Biopsy	2 nd Biopsy	Institution
	_____ MM / YYYY	_____ MM / YYYY	
MCNS (minimal change nephrotic syndrome)	<input type="checkbox"/>	<input type="checkbox"/>	
FSGS (focal segmental glomerulosclerosis)	<input type="checkbox"/>	<input type="checkbox"/>	
Other: _____	<input type="checkbox"/>	<input type="checkbox"/>	

Patient's Name: _____

II. Treatment

1. Corticosteroids Yes No
- Steroid sensitive Complete response
Relapse Yes No
- Partial response
Relapse Yes No
- Steroid resistant

2. Cytotoxic drugs Yes No Cyclosporine Yes No
- Name of drug: _____ Clinical response: _____
- Clinical response: _____

3. Dialysis / Renal Transplantation MM / YYYY
- Date of end stage renal failure: _____ / _____
- 1st transplantation: _____ / _____
- 2nd transplantation: _____ / _____
- Unsuccessful transplantation because of:
- Recurrence
- Graft loss because of:
- Recurrence
- Rejection
- Date of transplant failure: _____MM/_____YYYY

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 | <input type="checkbox"/> Facial dysmophy | <input type="checkbox"/> Heart anomalies |
| <input type="checkbox"/> Microcephaly | <input type="checkbox"/> Hexadactylia | <input type="checkbox"/> Allergies |
| <input type="checkbox"/> Mental retardation | <input type="checkbox"/> Spondyloepiphyseal dysplasia (Schminke-disease) | <input type="checkbox"/> Other: _____ |

IV. Remarks

Thank you very much for your assistance.

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

Name: _____
Address: _____

Phone: _____
Fax: _____

Address: _____ eMail: _____

BLOOD SAMPLE COLLECTION FOR MUTATIONAL ANALYSIS

- 1. Please call us** or send us an email to the below mentioned address before, or at the time when shipping the samples, so we can be certain to receive them within 2 days or otherwise trace them.
- 2. Venipuncture:** Draw 5 ml **EDTA-blood** or **Na-Heparin** under **sterile** conditions (wear gloves, do not touch rim of tubes); **immediately invert tubes several times** to prevent coagulation. If syringes and tubes are being used **rinse syringe with Na-Heparin**.
- 3. Storage: Always keep blood samples at room temperature! (Never chill, never freeze!)**
- 4. Transport:** Send samples and filled-out forms: consent and clinical questionnaire (inside shipping envelope), customs forms (outside shipping envelope or package). Immediately address to the name below by the fastest route possible, e.g. **2-day Express Air Mail, Federal Express, DHL Worldwide Express**. Get a guarantee from the carrier to deliver samples to our destination **within 1-2 days** (regular air mail is much too slow for blood samples). Protect samples from the cold by wrapping them in gauze or packaging them in Styrofoam. Don't forget to contact us!

If you like, you can use one of our personal courier accounts. For information on the account numbers please contact Dr. Gil Chernin at gilc@med.umich.edu or Professor Friedhelm Hildebrandt at fhilde@umich.edu.

Thank you for your cooperation!

Send samples to:

Prof. Dr. med. F. Hildebrandt
University of Michigan
Department of Pediatrics
8220C MSRB III
1150 West Medical Center Drive
Ann Arbor, MI 48109-5646, US
Phone: 734-615-7285
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Invoice

Shipper:

Consignee:

F. Hildebrandt, MD
University of Michigan
Department of Pediatrics
8220C MSRB III
1150 West Medical Center Drive
Ann Arbor, MI 48109-5646
USA

Content:

1 Parcel containing:
Documents and human blood or DNA, **non hazardous,**
non toxic, non infectious, sample for laboratory use only,
no commercial value

\$ 1 value for customs purposes only.

Date / Signature