Inaccuracy of clinical phenotyping parameters for hypertensive nephrosclerosis

Linda Zarif1, Adrian Covic1,2, Sudha Iyengar3, Ashwini R. Sehgal1,3, John R. Sedor1,4 and Jeffrey R. Schelling1

1Department of Medicine, Case Western Reserve University School of Medicine, 2University Hospital ‘C. I. Parhon’ Iasi, Romania, 3Department of Epidemiology and Biostatistics, and 4Department of Physiology and Biophysics, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Abstract
Background. Multiple studies suggest that hypertension-induced end-stage renal disease (ESRD) is heritable. Identification of nephropathy susceptibility genes absolutely requires accurate phenotyping, but the clinical hypertensive nephrosclerosis (HN) phenotype is poorly characterized. We hypothesized that many patients with HN as the indicated cause of ESRD on the Health Care Financing Administration (HCFA) 2728 form, fail to satisfy stringent HN phenotyping criteria.

Methods. Since renal biopsy documentation of HN is uncommon, clinical parameters for HN phenotype were applied: family history of hypertension, left ventricular hypertrophy, proteinuria <0.5 g/day, and hypertension preceding renal dysfunction (Schlessinger et al., 1994) or urine protein:creatinine (prot:creat) ratio <2.0 and no evidence of other renal diseases (AASK Trial Group, 1997).

Results. ESRD patients (n=607, 73% African American, 25% Caucasian) were enrolled in a study to identify HN susceptibility genes. HN was the most common cause of ESRD according to HCFA 2728 forms (37% prevalence). Phenotyping of randomly selected patients with HN from the total cohort revealed that 4/100 subjects satisfied the Schlessinger criteria, and 28/91 African Americans met AASK criteria for HN. From these figures, the adjusted prevalence of HN was only 1.5–13.5%. Of patients that could not be phenotyped for HN, 14 were misdiagnosed, 14 had urine prot:creat >2.0, and insufficient data were available in the remainder. Four patients underwent renal biopsy, but histology from only one was consistent with HN. If the HN phenotype definitions are revised to exclude ‘hypertension preceding renal dysfunction’, or proteinuria limits, then 44/100 and 39/91 patients respectively satisfy clinical phenotyping parameters for HN.

Conclusions. (i) We provide the strongest evidence to date that HN is less frequent in an ESRD population than commonly assumed if strict clinical criteria are used; many patients clinically diagnosed with HN may have undetected, treatable renal disease from other causes; (ii) relaxing HN phenotype criteria may erroneously include patients with glomerular diseases and secondary hypertension; (iii) reliance on HCFA 2728 diagnoses will confound identification of HN susceptibility genes; (iv) to attain adequate statistical power for genotype analysis, rigorous HN phenotyping will require screening an extremely large number of patients, which can be reasonably accomplished only in a multi-centre trial design.

Keywords: diagnosis; ESRD; genes; hypertension; nephropathy; renal failure

Introduction

The major causes of morbidity and mortality in developed countries are hypertension-related diseases. Recent estimates indicate that 25% of the US population, and 35% of African Americans have elevated blood pressure [1]. In addition, the 1999 USRDS [2] report states that hypertensive nephrosclerosis (HN) is the second most common cause of end-stage renal disease (ESRD) in Caucasians (21% incidence) and the leading cause of ESRD in African Americans (34% incidence). Multiple studies demonstrate an even greater disparity in the rate of renal disease progression due to hypertension in African Americans compared to Caucasians with equivalent blood pressures [3,4]. Importantly, increased risk to African Americans for hypertension-induced ESRD persists even after statistical correction for environmental co-factors [5], suggesting a role for genetic predisposition to ESRD from hypertension. A genetic risk for hypertension-related renal disease is also supported by studies demonstrating familial clustering of hypertensive ESRD in African
The gene product(s) that confer hypertensive ESRD risk are unknown, although several reports suggest a pathophysiological role for vasoactive factors that induce renal ischaemia [9–11]. Well-designed genetic studies to correctly identify HN susceptibility genes will necessarily require accurate HN phenotyping [12,13]. Since patients in the US with suspected HN infrequently undergo renal biopsies, which is the standard for diagnosing HN, the major impediment to establishing a reliable HN phenotype has been the lack of surrogate, clinical criteria that distinguish HN from other parenchymal renal diseases with associated secondary hypertension. Moreover, several studies have suggested that many patients assigned a diagnosis of HN may actually represent a heterogeneous group with renal artery stenosis, cholesterol microembolization, and other glomerular diseases [13,14]. Use of surrogate clinical parameters to diagnose HN in the US may almost entirely account for the variability in HN prevalence between large ESRD registries (USRDS, 25%; EDTA, 12%; Australia, 9%) [2,15].

Because of the large body of evidence suggesting genetic predisposition to hypertensive ESRD [16], and paucity of data regarding specific genes regulating this risk, we have initiated a large trial to identify susceptibility loci for HN by genotype analysis using whole genome scan and candidate gene approaches [17]. This endeavour requires identification of families with accurately diagnosed causes of ESRD, because inclusion of patients with heterogeneous aetiologies of nephropathy will confound statistical analysis and reduce the likelihood that disease alleles with major effects can be identified. Since renal biopsy documentation of HN is uncommon in the US, the aim of the current study is to determine a more accurate prevalence of HN by applying carefully defined clinical phenotyping criteria to a representative, dialysis patient sample. We hypothesized that the nephrologist-assigned diagnosis at initiation of dialysis overestimates HN prevalence, which is problematical for genetic analysis. Furthermore, many patients erroneously diagnosed with HN may have undetected renal diseases from other causes, and may therefore benefit from more than anti-hypertensive therapy.

Subjects and methods

Patient population

The initial study population pool included all ESRD patients from nine haemodialysis units in the north-east Ohio area (n = 3100). Patients while on dialysis were approached by trained interviewers, and asked to answer a screening questionnaire concerning their medical history and family history of renal disease and hypertension. From the population screened to date (n = 908), initial interviews were conducted in 607 consenting patients (73% African American, 25% Caucasian, 2% other). The most common reasons for not granting consent were mental impairment that prevented comprehension of the questions, or language barriers. The total number of patients was initially screened for a diagnosis of HN from Health Care Financing Administration (HCFA) 2728 forms. Completion of HCFA 2728 forms is mandatory in the US before reimbursement for renal replacement therapies, and required information includes the primary cause of renal disease, co-morbid conditions, and demographic data. Each form must be signed by a nephrologist, which implies agreement with the cause of ESRD. From this cohort, a subset with complete medical records was randomly selected for phenotype analysis (n = 100). All medical record volumes (paper and microfilm) were then reviewed for HN phenotyping data according to criteria described below. The protocol was approved by Institutional Review Boards from MetroHealth Medical Center, University Hospitals of Cleveland and Cleveland Clinic Foundation.

HN phenotyping criteria

ESRD patients were phenotyped for HN according to parameters established from two rigorously designed HN phenotyping studies [18,19]. HN phenotype criteria derived from Schlessinger et al. [18] included (i) family history of hypertension (first degree relative), (ii) left ventricular hypertrophy by echocardiography and/or electrocardiogram, (iii) proteinuria (<500 mg/24 h or ≤2 + on dipstick urinalysis), (iv) hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg) preceding any evidence of renal disease (proteinuria or serum creatinine >1.2 mg/dl), and (v) absence of nephrotoxic exposure, congenital or intrinsic renal disease, or systemic illness associated with renal damage. AASK Trial Group clinical phenotype criteria for HN, which correctly predicted HN in 38 of 39 African American patients with suspected HN who underwent diagnostic renal biopsy [19], included (i) age between 18 and 70 years, (ii) diastolic blood pressure >95 mmHg, (iii) urine protein to urine creatinine ratio <2.0, and (iv) no evidence of immune complex disease or diabetes mellitus.

Statistics

Comparison of ESRD family history prevalence in subjects phenotyped for HN vs subjects who could not be phenotyped for HN was made by two-tailed Student’s t-test. Statistical significance is defined as P < 0.05.

Results

ESRD diagnoses in the study population

Demographic data describing the entire dialysis population in Northeast Ohio (n = 3100), ESRD patients screened to date (n = 607), and the subpopulation with putative HN diagnoses analysed for this study (n = 100) are shown in Table 1. Notable is the preponderance in the screened population of African Americans, which primarily reflects the urban location of the participating dialysis centres. HN was the most common cause of ESRD in the overall population according to HCFA 2728 forms, with diabetic nephropathy the second most prevalent aetiology of ESRD (Table 2). These data are consistent with the 1999 USRDS report, which cites a 24.5% prevalence and...
Inaccuracy of hypertensive nephrosclerosis phenotyping parameters

Table 1. ESRD population demographics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Sex (% male)</th>
<th>Race (% CA/AA/Other)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ESRD population*</td>
<td>3100</td>
<td>51</td>
<td>51/46/3</td>
</tr>
<tr>
<td>ESRD patients screened</td>
<td>607</td>
<td>48</td>
<td>73/25/2</td>
</tr>
<tr>
<td>ESRD patients with HN*</td>
<td>220</td>
<td>52</td>
<td>12/87/1</td>
</tr>
<tr>
<td>HN study population</td>
<td>100</td>
<td>47</td>
<td>8/91/1</td>
</tr>
</tbody>
</table>

CA, Caucasian; AA, African American.
*North-east Ohio.

From HCFA 2728 forms.

26.6% incidence of ESRD due to hypertension [2], as well as with Bleyer et al. [20], who noted a 24 and 38% prevalence of ESRD due to hypertension in Caucasians and African Americans respectively. The relatively high prevalence of hypertensive ESRD in our study may reflect the large number of African Americans in our study population, as well as the recognition that HN incidence (according to the HCFA database) is increasing, and may now represent a larger proportion of the ESRD population.

HN diagnosis by strict phenotyping criteria

From the total pool of ESRD patients with a HCFA 2728 form-designated diagnosis of HN, 100 subjects were randomly selected for detailed phenotype analysis according to clinical criteria described in Subjects and methods. Subset phenotype analysis revealed that only four of 100 subjects satisfied the Schlessinger criteria for HN (Table 3). Because the AASK Trial Group restricted HN phenotype parameters to African Americans, the appropriateness of phenotyping non-African American patients using these criteria is unclear. Hence, AASK criteria were only applied to the 91 African American patients in our ESRD population. Within this cohort, 28 of 91 patients met AASK criteria for HN (Table 4).

Reasons for difficulty phenotyping HN

The reason for the inability to establish a HN phenotype in most patients, using either set of criteria, was insufficient data (Tables 3, 4), despite exhaustive medical record reviews that included a comprehensive search of the earliest available records in all patients.

Particular difficulty was encountered with documentation of the ‘hypertension prior to onset of renal insufficiency’ component of the Schlessinger criteria. Of the 82 subjects not meeting this criterion, most presented with hypertension and advanced renal disease upon entry into the medical care system, often requiring acute dialysis at the initial visit. In addition, HN phenotyping by AASK criteria was confounded in many instances by documentation of a urine protein:urine creatinine ratio greater than 2.0 or confirmation of kidney diseases other than HN (Table 5).

Alternative diagnoses in patients misclassified with HN

Although a definitive HN diagnosis requires a diagnostic renal biopsy, only four of the 100 patients in our series underwent renal biopsy. As defined by the study design, all four patients were assigned the diagnosis of HN on HCFA 2728 forms. However, histology from only one biopsy was consistent with HN. Focal segmental glomerulosclerosis, IgA nephropathy, and chronic interstitial nephritis were diagnosed in the other three patients. In addition to these three patients, many other subjects were diagnosed with HN despite clinical information indicating another diagnosis was more appropriate. The complete list of misdiagnosed patients, including the correct diagnoses, is shown in Table 5.

Introduction of potential biases in the phenotyping process

Since our long-term goal is to determine HN susceptibility loci by whole-genome scanning of DNA samples from HN probands and siblings [17], strict phenotyping criteria could disproportionately exclude patients with a family history of renal disease, and thereby increase the number of patients to be screened for adequate statistical power. This was considered unlikely, particularly with respect to Schlessinger criteria, because one parameter is a family history of hypertension, which might therefore preferentially include patients with a family history of renal disease. To address the possibility of a family history bias, the prevalence of ESRD family history (living sibling or parent receiving renal replacement therapy) was compared in patients with and those without a HN phenotype by Schlessinger or AASK criteria. Of the 30

Table 2. Causes of ESRD (from HCFA 2728 forms)

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>Overall prevalence (%)</th>
<th>Prevalence by race (% CA/AA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>220</td>
<td>36.9</td>
<td>21.8/43.9</td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>203</td>
<td>30.8</td>
<td>31.4/30.5</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>82</td>
<td>14.0</td>
<td>14.1/13.9</td>
</tr>
<tr>
<td>Diabetes mellitus type 1</td>
<td>21</td>
<td>6.0</td>
<td>9.5/4.4</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>4</td>
<td>2.0</td>
<td>4.9/0.7</td>
</tr>
<tr>
<td>Other</td>
<td>77</td>
<td>10.3</td>
<td>18.3/6.6</td>
</tr>
<tr>
<td>Total</td>
<td>607</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CA, Caucasian; AA, African American.
with Schlessinger HN phenotype criteria, the overall prevalence of 25%, which was obtained from the Using Incorrect diagnosis

Prior to obtaining HN phenotyping data using

**Implications for design of the HN genetic susceptibility study**

Prior to obtaining HN phenotyping data using Schlessinger and AASK criteria, our power analysis predicted that screening of 2500 ESRD patients would be required to enrol 150 sib pairs concordant for hypertension and HN and 100 sib pairs concordant for hypertension, but discordant for HN, for genetic analyses. This calculation was derived from a HN prevalence of 25%, which was obtained from the USRDS database [2]. When patients were screened with Schlessinger HN phenotype criteria, the overall prevalence of HN in our ESRD population (Caucasian and African American) was only 1.5% (36.9% prevalence from HCFA 2728 forms × 4/100 meeting HN phenotype criteria = 1.5%). Even if data from the AASK criteria is applied to the high-risk African American population, the prevalence of well-phenotyped HN patients was only 13.5% (43.9% prevalence in African Americans from HCFA 2728 forms × 28/91 meeting HN phenotype criteria = 13.5%). Using ‘corrected’ HN prevalence figures derived from Schlessinger criteria, the adjusted estimate is that nearly 42,000 ESRD subjects (Caucasian and African American) would need to be screened to obtain 250 affected and discordant sib pairs (24.6% overall HN prevalence (from USRDS)/corrected 1.5% HN

<table>
<thead>
<tr>
<th>Table 3. HN phenotype classification according to Schlessinger criteria*</th>
<th>n</th>
<th>Sex (M/F)</th>
<th>Race (CA/AA/other)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HN phenotype criteria met</td>
<td>4</td>
<td>1/3</td>
<td>2/3/0</td>
</tr>
<tr>
<td>Insufficient data to phenotype</td>
<td>42</td>
<td>21/21</td>
<td>2/39/1</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>22/24</td>
<td>2/39/1</td>
</tr>
</tbody>
</table>

CA, Caucasian; AA, African American.

*Schlessinger criteria: family history of hypertension (first-degree relative); left ventricular hypertrophy by echocardiography and/or electrocardiogram; proteinuria (<500 mg/24 h or ≤2+ on dipstick urinalysis); hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg) preceding any evidence of renal disease (proteinuria or serum creatinine >1.2 mg/dl); absence of nephrotic proteinuria, congenital or intrinsic renal disease, or systemic illness associated with renal damage.

**See Table 5 for details.

**Table 4. HN phenotype classification according to AASK Trial criteria**

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy*</td>
<td>2</td>
</tr>
<tr>
<td>Chronic pyelonephritis*</td>
<td>2</td>
</tr>
<tr>
<td>Acute glomerulonephritis*</td>
<td>2</td>
</tr>
<tr>
<td>Renal cell carcinoma*</td>
<td>2</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis*</td>
<td>1</td>
</tr>
<tr>
<td>IgA nephropathy*</td>
<td>1</td>
</tr>
<tr>
<td>Chronic interstitial nephritis*</td>
<td>1</td>
</tr>
<tr>
<td>HIV nephropathy*</td>
<td>1</td>
</tr>
<tr>
<td>Malignant hypertension*</td>
<td>1</td>
</tr>
<tr>
<td>Myeloma kidney*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Both patients with hyperglycaemia and hypertension for more than 10 years prior to starting dialysis.

**Table 5. Established causes of ESRD in patients inappropriately diagnosed with HN**

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic interstitial nephritis</td>
<td>1</td>
</tr>
<tr>
<td>HIV nephropathy</td>
<td>1</td>
</tr>
<tr>
<td>Malignant hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

*See Table 5 for more details.

**Only African Americans were included.**
prevalence × 2500 ESRD patients (from power analysis) = 41 667 ESRD patients. Because screening such a large number of patients would be a difficult task, and assuming that HN is rare in the Caucasian population [21], an alternative approach is to restrict recruitment to African Americans that meet AASK criteria. Even this approach would require screening over 6000 African American patients to obtain the requisite sample size (33.8% HN prevalence in African Americans (USRDS)corrected 13.5% HN prevalence × 2500 ESRD patients (from power analysis) = 6259 African American ESRD patients). Although screening 6000 African American ESRD subjects is more feasible than screening 42 000 ESRD patients with multiple ethnicities, it is clear that identification of HN susceptibility genes by either strategy can only be reasonably accomplished in a multi-centre trial design.

Discussion

Recent studies indicate that HN may be the most common cause of ESRD, particularly within the African American population [2,21]. Although blood pressure control is important, anti-hypertensive therapy alone is often insufficient to prevent HN progression to ESRD [21], suggesting that additional factors participate in progressive HN pathogenesis. Published data support the premise that HN susceptibility genes regulate renal tissue injury in response to hypertension. The HDFP and MRFIT trials showed that loss of kidney function was greater in African Americans than in Caucasians, despite comparable levels of diastolic blood pressure [3,22]. Secondary analyses from the MDRD study demonstrated that, after controlling for baseline co-variables, the rate of GFR decline was approximately 1 ml/min/year greater in African Americans compared to Caucasians with equivalent mean arterial pressures greater than 98 mmHg [4], suggesting that susceptibility gene effects may only be apparent when blood pressure control is not optimal in at-risk African Americans. Finally, multiple studies have demonstrated a familial risk of ESRD from hypertension [6–8,16], suggesting that family-based genetic approaches may enhance the probability of HN susceptibility gene discovery.

We have initiated a trial that aims to identify HN susceptibility gene(s) using two different sets of clinical criteria that best characterize the HN phenotype [18,19]. When these phenotyping parameters were applied to a dialysis population, the diagnosis of HN could not be confirmed in most patients, a finding consistent with divergent estimates of HN incidence that have resulted from differences in diagnostic criteria [14,15]. At one extreme are prospective, longitudinal studies of hypertensive patients [23–25], which conclude that the incidence of HN is negligible. At the other extreme are USRDS figures, which indicate that HN is the most common cause of ESRD, with an incidence of 26.6% [2]. While this disparity in HN incidence may partly reflect differences in ESRD study populations or renal biopsy frequencies between countries, our data support the additional possibilities that stringency of diagnostic criteria and misdiagnosis contribute to phenotype misclassification.

Though abstraction of diagnoses from standardized forms generated for financial purposes may be adequate for other projects, one conclusion from our study is that information from HCFA 2728 forms is inadequate for diagnosing HN. In contrast to other diseases that can be definitively phenotyped clinically, HN requires a biopsy, but is generally a diagnosis of exclusion in the US, often based on no criteria other than co-existing ESRD and hypertension in the absence of other known renal diseases. To highlight the subjectivity of diagnosing HN clinically, Perneger et al. [26] noted that US physicians are twice as likely to diagnose HN in an African American patient compared to a Caucasian patient with an otherwise identical case history. Our data are consistent with this finding, inasmuch as 73% of our dialysis patient population is African American, yet 93% of the subjects with insufficient data or incorrect diagnosis of HN were African American, and the prevalence of HN by HCFA 2728 forms was approximately twice as great in African Americans compared to Caucasians (see Table 2). Because the HN cohort contained few Caucasian subjects, the conclusions of this study may be applicable only to African Americans, and additional studies with larger numbers of Caucasians will be necessary to validate results in this ethnic group.

The lower prevalence of HN compared to the HN prevalence derived from HCFA 2728 forms resulted primarily from application of strict surrogate clinical criteria to our prevalent ESRD population. In many cases in which the HN phenotype could not be established, we speculate that HN was diagnosed by default in ESRD patients with undiagnosed renal diseases other than HN and secondary hypertension. Inaccuracy of HCFA 2728 form diagnoses also raises the possibility of ‘false negative’ HN patients. Since the study was designed to recruit only patients with presumed HN, the false negative frequency could not be calculated. However, because most reports in the HN literature indicate that over-diagnosis is the major problem [14,18], the number of false negatives is likely to be small.

Although a significant rate of misdiagnosis was detected in our study, the most common problem with HN phenotyping was insufficient data. Even when all medical records were exhaustively reviewed, all diagnostic criteria could not be fulfilled in most cases, since many patients presented with advanced renal disease, and had few diagnostic tests prior to starting dialysis. To avoid exclusion of true HN patients, one could consider loosening the clinical criteria. For example, if ‘hypertension preceding renal dysfunction’ is omitted from the Schlessinger HN phenotype definition, 44 of 100 patients then satisfy clinical phenotype criteria for HN, rather than four of 100 with the original, more stringent criteria. However, revising the
Schlessinger criteria could include patients with secondary hypertension from renovascular or parenchymal renal disease to be erroneously included in the HN group. Since Bleyer et al. [20] demonstrated a strong correlation between atherosclerosis and hypertensive ESRD, and 20 of 44 patients meeting the revised Schlessinger criteria for HN also had a history of atherosclerosis (data not shown), many of these patients may have renovascular or atheroembolic renal disease, rather than HN. If the AASK Trial-based HN phenotype is revised to omit the ‘urine protein:creatinine ratio <2’ criterion, 39 of 91 patients would then satisfy the criteria for HN, compared to 28 of 91 when the proteinuria limit is considered. Nephrotic-range proteinuria has been reported in patients with biopsy-proven HN [27], which would justify revision of the proteinuria requirement in the HN phenotype. However, proteinuria generally does not exceed 0.5 g/day [21], and the retrospective study design in the biopsy case series [27] is therefore likely to be biased toward selection of patients with a biopsy indication, such as those with significant proteinuria. Furthermore, raising the maximum urine protein criterion in the HN phenotype definition increases the probability of recruiting patients with other glomerular diseases and hypertension.

An alternative to phenotyping HN in dialysis patients using surrogate clinical parameters is to require a renal biopsy, which is diagnostic for HN. Although this strategy would undoubtedly enhance HN phenotyping specificity, it would require identification of HN subjects earlier in the disease course, since interpretation of biopsies from long-standing ESRD patients is likely to be confounded by global sclerosis and arteriolar pathology from secondary hypertension. Because progression to ESRD is a severe phenotype, and inclusion of these subjects would enrich the population for HN genes, biopsy-proven HN subjects might then require long-term follow-up in a prospectively designed trial. Although this would be more cumbersome than identifying probands by clinical phenotyping criteria extracted from past medical records, it is an alternative approach that we are considering.

One ramification of HN over-diagnosis is the misperception that a large percentage of the ESRD population has a disease for which the sole treatment is blood pressure control. However, many of these patients may have parenchymal renal diseases, such as unrecognized accelerated hypertension, renal artery stenosis, or primary renal microvascular diseases with hypertensive manifestations, which are amenable to other therapies. Another major but less widely recognized implication from our study is that genetic approaches to understanding HN disease pathophysiology (which will become more commonplace once the entire human genome is sequenced) will require careful scrutiny of clinical diagnoses before assigning phenotypes to study subjects [12]. This is especially true if nephropathy susceptibility genes with major phenotypic effects are unique to specific renal diseases, rather than a common component to multiple renal diseases. Based upon the results of this study, we conclude that successful identification of HN susceptibility genes will require either screening a very large number of ESRD patients for a clinically defined HN phenotype or a prospective trial of biopsy-proven HN subjects. Either strategy is beyond the scope of what can be accomplished in our own patient population, and will therefore require a multi-centre effort.

Acknowledgements. This work was supported by grants from the National Institutes of Health (DK54644, DK54178, DK38558, DK51472, DK02281, DK57329), Northeast Ohio chapter of the American Heart Association, Central Ohio Diabetes Association, Leonard Rosenberg Foundation, Juvenile Diabetes Foundation, and Baxter Extramural Grant Program. Portions of this work were presented at the 32nd Annual American Society of Nephrology meeting, Miami, FL, 1999. Dr. Schelling is an Established Investigator of the American Heart Association.

References
Inaccuracy of hypertensive nephrosclerosis phenotyping parameters


Received for publication: 25.1.00
Accepted in revised form: 3.7.00