J Am Soc Nephrol 9: 1270–1276, 1998

Familial Aggregation of Renal Disease in a Population-Based Case-Control Study

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Abstract. Family history of renal disease has been associated with an increased risk of end-stage renal disease (ESRD). It is uncertain whether this risk is mediated by familial aggregation of risk factors for ESRD, such as diabetes and hypertension. The association of ESRD with familial aggregation of renal disease was examined in a large, population-based case-control study conducted in Maryland, Virginia, West Virginia, and Washington, DC. The number of first-degree relatives who were affected with any type of renal disease was compared between 689 newly treated ESRD patients registered in the Medicare ESRD program (92% of all eligible incident cases presenting between January and July of 1991) and 361 control subjects without ESRD who were selected by random-digit dialing (90% response rate). Patients and control subjects were frequency matched by age; patients with ESRD caused by polycystic kidney disease and other known hereditary kidney diseases were excluded. Analysis was conducted using multiple logistic regression. After controlling for the proband's age, gender, race, family size, socioeconomic status, and personal and family histories of diabetes and hypertension, having one first-degree relative with renal disease increased the odds of ESRD by 1.3 (95% confidence interval, 0.7 to 2.6) and having two or more affected first-degree relatives increased the odds of ESRD by 10.4 (95% confidence interval, 2.7 to 40.2). These data support familial aggregation of renal disease in excess of that predicted by clustering of diabetes and hypertension within families, suggesting that either genetic susceptibility or environmental exposures shared within families increase the risk of developing ESRD. This risk is also much higher when two or more first-degree relatives have renal disease. Unraveling the molecular basis of this increase in risk may provide new avenues for treatment and prevention of ESRD.

The age-adjusted incidence rate of treated end-stage renal disease (ESRD) in the United States has increased approximately 10% per year since 1986. In 1995, more than 255,000 patients were treated for ESRD, yielding a crude prevalence rate of 967 per million (1). In addition to the societal burden, the poor prognosis associated with ESRD argues for a better understanding of its cause and prevention. Genetic mutations are known to cause hereditary nephropathies such as polycystic kidney disease and Alport's syndrome, which lead to a high risk of chronic renal failure (2–4). However, these diseases are rare and account for relatively small percentages of the total number of ESRD patients in the United States (2.7% cystic kidney diseases and 0.2% Alport's syndrome) (1).

Identifying a genetic mechanism for the majority of ESRD cases would have important implications for public health. Several studies have already shown a strong association between family history of ESRD and increased risk of ESRD, suggesting a hereditary component to the disease (5–9). This association may also be stronger in blacks (6,8) than whites (9), indicating specific ethnic differences. Explanations for the clustering of ESRD in families include the sharing of specific genes, environmental exposures, or underlying diseases among family members. In families with a higher number of members affected with ESRD, it is unclear whether ESRD clusters independently of other inherited diseases such as diabetes and hypertension. It is especially important to consider diabetes and hypertension because they are the underlying causes of ESRD in 37% and 29% of incident ESRD cases, respectively (5). The familial risk of ESRD, therefore, may be due to an inherited susceptibility to kidney damage or the aggregation of ESRD risk factors within families. To identify familial clustering of ESRD caused by genetic risk factors, the effects of shared environmental exposures, as well as the clustering of diabetes and hypertension in families, should be controlled.

To examine the association between family history of renal disease and ESRD, independent of the aggregation of diabetes and hypertension, we conducted a large, population-based case-control study in Maryland, Virginia, West Virginia, and

Received May 21, 1997. Accepted January 14, 1998.
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1046-6673/0907-1270$03.00/0
Journal of the American Society of Nephrology

Washington, D.C., with uniform data collection instruments and a standardized family history questionnaire. Information on parents, siblings, and children regarding diabetes, hypertension, and renal disease was collected in a similar manner from both patients and control subjects.

Materials and Methods

Study methods have been reported previously (10,11). As part of a population-based study of ESRD risk factors, 689 patients with newly onset ESRD not caused by polycystic kidney disease and 361 control subjects were recruited. The sampling frame included the residents of Maryland, Virginia, West Virginia, and Washington, DC.

Study Population

Incident ESRD patients receiving their initial renal replacement therapy between January and July of 1991 were identified by the Mid-Atlantic Renal Coalition. Patients were 20- to 64-yr-old individuals with ESRD who could be reached by phone. The patients had been receiving renal replacement therapy for a median of 5 mo at the time of the interview. Control subjects without ESRD were selected by random-digit dialing in the same geographic region as the patients. Of 1311 residences reached, 1259 (96%) were screened, and 402 were found to have one or more residents eligible to participate in the study. When several potentially eligible people lived in the same household, one was randomly selected and invited to participate. Of the eligible people, 361 (96%) were interviewed, 38 refused, and three interrupted the interview.

The ratio of patients to control subjects was 2:1, and control subjects were frequency matched to patients by 5-yr age groups. To maintain adequate statistical power to assess differences between subsets of ESRD, more patients than control subjects were needed. The number of patients was not a limiting factor in this study because the population was sufficiently large. Also, the selection of control subjects by random-digit dialing was labor-intensive, so we chose to limit the number enrolled to devote more resources to obtaining extensive information from each participant.

Data Collection

Initially, potential study subjects were contacted by letter. Subsequently, trained interviewers spoke to all potential participants by phone. Interviewers were aware of the participant's status as a patient or control subject but did not know the study's hypotheses. Before administering the interview, interviewers provided general information regarding the purpose of the study and obtained informed consent. The average interview lasted approximately 24 min.

Exposure Variables

The exposure variables of interest were age, gender, race, socioeconomic status, family history of ESRD and other renal diseases, and family and personal history of hypertension and diabetes. Race was self-reported and categorized for analysis into white, black, or other. Information on socioeconomic status was collected specifically asking for education level completed, income level, dental status as indicated by the number of filled teeth, and type of health insurance. Family history was collected for a participant's mother, father, siblings, and children. Family history of kidney diseases other than ESRD included family members with polycystic kidney disease, a variety of specified disorders, and unknown kidney diseases. Family history of ESRD and other renal diseases was also consolidated into one category of all renal diseases. Personal history of hypertension included information regarding duration of (greater or less than 15 yr) and hospitalization for hypertension. Personal history of diabetes also included information regarding duration (greater or less than 15 yr) and type of diabetes mellitus.

Statistical Analyses

Family history of renal diseases was compared between patients and control subjects, using multiple logistic regression analysis to simultaneously control for potential confounders. The analysis controlled for factors that increase the risk of ESRD such as male gender, black race, and personal medical history of diabetes and hypertension. In addition, family history of diabetes and hypertension was hypothesized to increase the clustering of renal disease within families, so these variables were included in the model. Adjustment for the number of family members was performed to account for the difference in family size between patients and control subjects. Odds ratios and 95% confidence intervals were estimated and approximate the relative risks in this context. In race-stratified analyses in which one of the cells had zero patients, 0.5 was added to all cells to allow for estimation of the odds ratio. P values <0.05 were considered statistically significant. SAS statistical analysis software was used to estimate the odds ratios and perform hypothesis testing (12).

Results

Sample Description

More men and blacks were present among patients than among control subjects (Table 1). Because patients and control subjects were frequency matched by 5-yr age groups, the distribution of age among the two groups was similar. Patients with a personal history of diabetes and hypertension outnumbered the corresponding control subjects. The mean number of children per household was the same for patients (2.3) and control subjects (2.3). However, family size was slightly larger among the patients. Patients had an average of 4.1 siblings and 8.4 family members, whereas control subjects had an average of 3.3 siblings and 7.6 family members ($P < 0.01$).

Univariate Analyses

First, analyses were performed that examined the relationship between a family history of renal disease and the risk of ESRD without controlling for other variables (Table 2, crude odds ratios). Family history of any renal disease was associated with a greater risk of ESRD (Table 2). Individuals who had only one relative with a history of any renal disease had a 1.37 higher odds of ESRD, whereas those with two or more relatives with any renal disease had over a threefold greater odds of ESRD. A similar pattern of risk was seen with family history of ESRD. Family history of renal disease other than ESRD had a somewhat weaker association with risk of having ESRD in unadjusted analyses.

Multivariate Analyses

In analyses that controlled for age, gender, and race, the results were very similar to the univariate results. Regardless of the definition (ESRD, renal disease other than ESRD, or any renal disease), a more positive family history was associated with an increasing odds of ESRD (Table 2). Additional adjustment for family size had very little effect on the odds ratios

Table 1. Demographic characteristics of participants in the Mid-Atlantic end-stage renal disease case-control study, 1991[a]

Characteristic	Patients (n = 690) n (%)	Control Subjects (n = 361) n (%)
Gender[b]		
male	393 (57.0)	126 (34.9)
female	297 (43.0)	235 (65.1)
Race[b]		
white	290 (42.0)	303 (83.9)
black	380 (55.1)	51 (14.1)
other	19 (2.8)	7 (1.9)
no answer	1 (0.1)	0 (0.0)
Age[b,c]		
<20 yr	6 (0.9)	2 (0.6)
20 to 24 yr	15 (2.2)	10 (2.8)
25 to 29 yr	45 (6.5)	20 (5.5)
30 to 34 yr	74 (10.7)	34 (9.4)
35 to 39 yr	54 (7.8)	33 (9.1)
40 to 44 yr	77 (11.2)	44 (12.2)
45 to 49 yr	68 (9.9)	38 (10.5)
50 to 54 yr	99 (14.4)	56 (15.5)
55 to 59 yr	111 (16.1)	55 (15.2)
60 to 64 yr	131 (19.0)	63 (17.5)
≥65 yr	10 (1.5)	6 (1.7)
Income ($)[b]		
<10,000	214 (31.0)	36 (10.0)
10 to 19,999	175 (25.4)	50 (13.8)
20 to 39,999	150 (21.7)	117 (32.4)
≥40,000	97 (14.1)	137 (38.0)
no answer	54 (7.8)	21 (5.8)
School (yr)[b]		
≤6	42 (6.1)	7 (1.9)
7 to 11	212 (30.7)	52 (14.4)
12	234 (33.9)	127 (35.2)
13 to 16	164 (23.8)	125 (34.6)
≥17	38 (5.5)	49 (13.6)
no answer	0 (0.0)	1 (0.3)
Dental care[b,d]		
no teeth	134 (19.4)	35 (9.7)
no fillings	277 (40.1)	51 (14.1)
1 to 4	129 (18.7)	80 (22.2)
5 to 8	81 (11.7)	85 (23.5)
≥9	62 (9.0)	104 (28.8)
no answer	7 (1.0)	6 (1.7)
Insurance status[b]		
private	365 (52.9)	221 (61.2)
HMO	72 (10.4)	74 (20.5)
Medicare	57 (8.3)	20 (5.5)
Medicaid	100 (14.5)	7 (1.9)
none	95 (13.8)	37 (10.2)
no answer	1 (0.1)	2 (0.6)
Diabetes mellitus[b]		
none	359 (52.0)	335 (92.8)
type 1	155 (22.5)	4 (1.1)
type 2	176 (25.5)	22 (6.1)
Hypertension (duration of diagnosis)[b]		
none	71 (10.3)	259 (71.7)
≤15 yr	447 (64.8)	82 (22.7)
>15 yr	172 (24.9)	20 (5.5)

[a] Excluding cases with polycystic kidney disease.
[b] $P < 0.001$.
[c] Patients and control subjects were frequency matched by 5-yr age groups.
[d] Number of filled teeth based on self-inspection in mirror.

(data not shown). Measures of socioeconomic status were also modeled. Only income level and dental care were significant predictors of ESRD risk. These socioeconomic factors affected the odds ratios of a positive family history only slightly and did not change the overall significant trend of positive odds ratios for ESRD associated with a positive family history.

Final adjustment for age, gender, race, family size, socioeconomic status, and relevant personal and family history resulted in a large disparity in risk between those with only one first-degree relative with any renal disease compared to those with two or more. This increase in the odds of ESRD among individuals with two or more affected relatives was also observed for family history of ESRD and other renal disease. Examination of the data revealed that this occurred because a strong family history of renal disease (two or more affected relatives) was more frequent among patients than control subjects without a personal history of diabetes and hypertension. Thus, controlling for the personal history of diabetes and hypertension resulted in a stronger association with ESRD.

Stratified Analyses

To examine the hypothesized interaction of family history with race, analyses were stratified by race (Table 3). Family history of renal disease was associated with risk of ESRD in both whites and blacks. The associations were similar in both groups for unadjusted and adjusted analyses. In the fully adjusted model, the odds of ESRD for those with one relative with renal disease compared to those with none was 1.1 (95% confidence interval [CI], 0.5 to 2.5) in whites and 1.7 (95% CI, 0.6 to 5.2) in blacks. For those with two or more relatives with renal disease, the odds ratio was 7.4 (1.7 to 31.5) in whites and was infinite (could not be estimated) in blacks, because there were no black control subjects with two or more relatives with renal disease. The increase in odds of ESRD associated with an increasing number of affected relatives occurred in both whites and blacks (trend tests, $P = 0.03$). Formal testing for interaction could not reject the hypothesis that the risk factors family history of renal disease and race were similar ($P = 0.81$). However, the power to detect an interaction was limited because the study was not matched on race (only 51 black control subjects).

Table 2. History of renal disease, diabetes mellitus, and hypertension in first-degree relatives of ESRD patients and population control subjects, Mid-Atlantic Region, United States, 1991[a]

Relatives with	Patients *n* (%)	Control Subjects *n* (%)	Crude Odds Ratios (95% CI)	Odds Ratios Adjusted for Age, Gender, and Race (95% CI)	Odds Ratios Adjusted for Age, Gender, Race, Family Size, Socioeconomic Status, and Relevant Personal and Family History[b] (95% CI)
Any renal disease					
none	578 (83.9)	320 (88.9)			
1	89 (12.9)	36 (10.0)	1.37 (0.91 to 2.07)	1.24 (0.78 to 1.96)	1.34 (0.68 to 2.65)
≥2	22 (3.2)	4 (1.1)	3.05 (1.04 to 8.93)[c]	3.58 (1.15 to 11.17)[c]	10.37 (2.67 to 40.22)[d]
ESRD					
none	620 (90.0)	342 (95.0)			
1	57 (8.3)	16 (4.4)	1.97 (1.11 to 3.47)	1.46 (0.78 to 2.73)	0.95 (0.39 to 2.31)
≥2	12 (1.7)	2 (0.6)	3.31 (0.74 to 14.87)[d]	3.31 (0.67 to 16.38)	6.43 (1.13 to 36.63)
Renal disease other than ESRD					
none	640 (92.9)	337 (93.6)			
1	44 (6.4)	21 (5.8)	1.11 (0.65 to 1.89)	1.24 (0.68 to 2.26)	1.93 (0.79 to 4.70)
≥2	5 (0.7)	2 (0.6)	1.32 (0.25 to 6.83)	2.55 (0.44 to 14.33)	14.44 (1.99 to 104.61)[d]

[a] Excluding cases of polycystic kidney disease. ESRD, end-stage renal disease; CI, confidence interval.
[b] In addition to the variable of interest, the model included age, gender, race, family size, income level, dental care, duration of hypertension (none, ≤15 yr, >15 yr), hospitalization for hypertension, duration (none, ≤15 yr, >15 yr) and type of diabetes (1 or 2), and family histories of hypertension and diabetes mellitus.
[c] $P_{trend} < 0.05$.
[d] $P_{trend} < 0.01$.

Analyses were also stratified by age of onset in patients and by age at interview in control subjects to determine whether family history was more strongly associated with ESRD in individuals who developed ESRD earlier in life. After adjustment for all variables, the odds of ESRD associated with any family history of renal disease was 1.7 for subjects younger than 50 yr of age (95% CI, 1.0 to 3.0) and 2.0 for those 50 yr and older (95% CI, 1.1 to 3.8) compared with control subjects in the same age range. There was no significant interaction between age and family history of renal disease ($P = 0.82$).

A family history of diabetes or hypertension was associated with an increased risk of diabetes and hypertension in the study subjects themselves (odds ratios [OR]: 2.52 and 1.51, respectively). The degree to which a family history of diabetes or hypertension increased the risk of renal disease beyond the hypertension and diabetes status of the patient was examined in stratified analysis. Family history of diabetes was not significantly different between the diabetic ESRD patients and diabetic control subjects (OR = 0.9; 95% CI, 0.8 to 1.1). Similarly, the nondiabetic ESRD patients did not have a significantly higher family history of diabetes than nondiabetic control subjects (OR = 1.2; 95% CI, 0.9 to 1.5). There was also no difference in family history of hypertension between the hypertensive patients and hypertensive control subjects (OR = 1.0; 95% CI, 0.8 to 1.1), as well as between the nonhypertensive patients and nonhypertensive control subjects (OR = 0.9; 95% CI, 0.7 to 1.3). Thus, ESRD patients were more likely to have a family history of diabetes, hypertension, or both, than their corresponding control subjects, only because patients were more likely to be diabetic and/or hypertensive, not because they had ESRD.

Discussion

Our results show that familial aggregation of renal disease cannot be completely explained by clustering of diabetes and hypertension within families. Although the clustering of shared behavioral or environmental exposures leading to higher ESRD risk could not be assessed, these results suggest that there may be a genetic susceptibility to ESRD independent of that induced by diabetes and hypertension. In the final model that was adjusted for age, gender, race, family size, income level, dental care, personal history of diabetes and hypertension, and family history of diabetes and hypertension, the association between family history of renal disease and ESRD was observed for the overall population and independently in the white and black populations. The risk was particularly marked for a strong family history (greater than or equal to two first-degree relatives with renal disease). Thus, families with three or more members with renal disease are more likely to have an inherited genetic susceptibility. It is noteworthy that the risk conferred by having a family history of renal disease other than ESRD was similar to the risk conferred by a family history of ESRD. This finding suggests a common pathogenesis for both ESRD and the milder and more common forms of nephropa-

Table 3. History of renal disease in first-degree relatives of white and black ESRD patients and population control subjects, Mid-Atlantic Region, United States, 1991[a]

Relatives with	Patients *n* (%)	Control Subjects *n* (%)	Crude Odds Ratios (95% CI)	Odds Ratios Adjusted for Age and Gender (95% CI)	Odds Ratios Adjusted for Age, Gender, Family Size, Socioeconomic Status, and Relevant Personal and Family History[b] (95% CI)
Whites					
any renal disease					
none	251 (86.9)	271 (89.4)			
1	29 (10.0)	28 (9.2)	1.11 (0.64 to 1.92)	1.24 (0.70 to 2.19)	1.08 (0.47 to 2.48)
≥2	9 (3.1)	4 (1.4)	2.42 (0.74 to 8.00)	2.61 (0.76 to 8.91)	7.40 (1.74 to 31.52)[c]
Blacks					
any renal disease					
none	311 (81.8)	43 (86.0)			
1	56 (14.7)	7 (14.0)	1.13 (0.49 to 2.64)	1.18 (0.50 to 2.77)	1.73 (0.57 to 5.24)
≥2	13 (3.5)	0 (0.0)	3.77 (0.22 to 64.57)[d]	2.20 (0.28 to 16.96)[e]	∞[c]

[a] Excluding cases of polycystic kidney disease. Abbreviations as in Table 2.
[b] In addition to the variable of interest, the model included age, gender, family size, income level, dental care, duration of hypertension (none, ≤15 yr, >15 yr), hospitalization for hypertension, duration (none, ≤15 yr, >15 yr) and type of diabetes (1 or 2), and family histories of hypertension and diabetes.
[c] $P_{trend} < 0.05$.
[d] Odds ratio estimated by adding 0.5 to each cell.
[e] Mantel–Haenszel odds ratio adjusted only for gender and estimated by adding 0.5 to each cell.

thy. In addition, it suggests that the genetic basis and distribution of these diseases need to be studied further.

We also found that family history of diabetes and hypertension was associated with ESRD in univariate analysis, but this association disappeared after adjustment for personal history of these diseases. Individuals with ESRD, therefore, are no more likely to have relatives with diabetes and hypertension than individuals without ESRD who have the same personal history of diabetes and hypertension.

Familial clustering of ESRD has been reported in four previous case-control studies. In a study by Ferguson *et al.* (6), 26.3% of 114 patients compared with 11.1% of the corresponding 99 control subjects had a first- or second-degree relative who died from kidney disease or had chronic kidney failure. In a population-based study of 325 patients and 325 control subjects, having a parent, child, or sibling with renal disease (excluding kidney stones, trauma-induced kidney damage, or diabetic nephropathy) increased the odds of ESRD by 9.3 (7). Freedman *et al.* (8) found that among blacks having a first-degree relative with ESRD increased the odds of ESRD by 9.1; having a first- or second-degree relative with ESRD increased the odds by 5.2; and having a first-, second-, or third-degree relative with ESRD increased the odds by 4.6. Among whites, the odds ratios were lower: having a first-degree relative with ESRD increased the odds of ESRD by 2.8; having a first- or second-degree relative with ESRD increased the odds of ESRD by 2.7; and having a first-, second-, or third-degree relative with ESRD increased the odds of ESRD in the patients by 3.5 (9). The odds ratios reported in this study are lower than the aforementioned studies mainly because of the lower prevalence of renal disease among the relatives of patients. In this analysis, 11.1% of control subjects had a family history of renal disease, which was identical to the data reported by Ferguson *et al.* (6). This study finds that the excess risk is most prominent among people with two or more first-degree relatives with renal disease. In fact, after adjustment for age, gender, and race, having two relatives with renal disease other than ESRD was associated with a higher risk than having one relative with ESRD.

Of the studies examining familial clustering of renal disease, this study is one of the few that is population-based. The comprehensive definition of family history that includes ESRD and other forms of renal disease is important given the rarity of ESRD in the population. Examining family history of other renal diseases highlights a possible general susceptibility to all forms of kidney damage and dysfunction that is inherited. This study also provides valuable information on the association between ESRD and family history of renal disease, taking into account concurrent clustering of diabetes and hypertension in some families. Previous studies have shown that relatives of individuals with diabetic and hypertensive nephropathy have a higher prevalence of nephropathy compared with relatives of individuals with only diabetes or hypertension (1,5,8,13–16). By adjusting for family history of hypertension and diabetes, this study shows that there may be a unique genetic susceptibility to ESRD apart from susceptibility due to these underlying diseases.

Differences in gender and race distributions between patients and control subjects were observed. Patients and control subjects were not matched on these factors to study the effects of gender and race. The proportion of women among control

subjects was significantly higher (65%) than expected from 1980 U.S. Census (17) figures (52%). This finding was probably not due to selective refusals, because there were few of them, or to greater availability of women for telephone interviews, because the study participant was selected at random from among eligible household members whether present or not. The higher proportion of women may be caused by chance. Confounding by gender, however, was controlled by adjustment in the regression model.

There also were more whites among control subjects than predicted by the 1980 U.S. Census (84% *versus* 78%) and few blacks (14% *versus* 20%). This finding may have been caused by a lower availability of telephones among blacks. The excess of blacks among patients was expected from U.S. Renal Data System data (1), and the data in the study were consistent with previous suggestions (8) of a stronger genetic basis among blacks. However, the number of black control subjects in this study was too small to allow for definitive racial comparisons.

Differences in family size were also observed between patients and control subjects, which may be important because larger families have a greater probability of having clusters of any disease. In these population-based data, patients had a slightly higher number of siblings and family members than control subjects. However, the odds of ESRD remained constant after controlling for family size. The rarity of renal disease also makes it less likely that two or more affected individuals would occur by chance in one family. Therefore, the observed familial clustering of renal disease is most likely not due to chance.

Validation of the reported family history of renal disease was not possible in this study. Misclassification of disease status in both control subjects and reported affected family members may have masked the true magnitude of the association between family history of renal disease and ESRD. Although it is possible that control subjects may have renal insufficiency, population studies show that the prevalence of severe undetected chronic renal failure is low. Information on the disease status of family members may also be inaccurate, but if misclassification is random among patients and control subjects, the estimated odds ratios would be biased toward 1.0. On the other hand, if the family members of patients are more aware of the signs of renal disease and are providing more accurate information, then the odds ratios would be inflated. We attempted to reduce the magnitude of this information bias by limiting the history to parents, siblings, and children. In addition, recall bias was assessed by comparing family history of cancer between patients and control subjects. After adjusting by age, gender, and race, the odds of having relatives with cancer was not significantly different between patients and control subjects (OR = 0.8; 95% CI, 0.7 to 1.0). The same was true for history of diabetes and hypertension (after accounting for personal history). These results show that chronically ill patients and unaffected control subjects are equally likely to report a family history of serious illness. The validity of these data on family history is further substantiated by the similarity between the prevalence of renal disease in control subjects to another population-based study (6).

The distinction between genetic and familial environmental contributions to disease risk cannot be elucidated by this case-control analysis of the clustering of renal disease in families. Environmental risk factors for ESRD have been proposed that can be shared among family members. For example, families who are at a lower socioeconomic status might not seek or be able to afford treatment for diabetes, hypertension, or early symptoms of kidney damage because of limited access to health care (18–21). To account for differences in socioeconomic status, income level and access to dental care were included in the model. The inclusion of these variables, however, did not affect the association between ESRD and family history of renal disease. It is also uncertain to what extent other risk factors for ESRD, such as acetaminophen and nonsteroidal anti-inflammatory drug use (10), lead exposure (22), and infectious agents (23–26), cluster in families.

If the observed familial clustering is due to shared genes, several genetic parameters may have diluted our findings. The presence of a susceptibility gene does not ensure the development of disease. For most genes, a proportion of individuals who carry the susceptibility allele will not develop the disease, and some genes are not sufficient to cause disease without interacting with other genetic or environmental factors. This incomplete penetrance would diminish familial clustering of disease. Variability in gene expression may also have diluted our findings, because many family members of ESRD patients who express early signs of kidney damage such as microalbuminuria, proteinuria, or mild renal insufficiency are likely to have been labeled as unaffected.

In conclusion, this investigation of the genetic contribution to ESRD shows that family history of renal disease seems to be associated with ESRD. In addition to case-control studies of family history, data from twin studies of identical and nonidentical twins would be valuable in identifying the relative importance of genetic factors. Unfortunately, studies of siblings are difficult to do because the number of concordant pairs in the population is extremely low. Pedigree data collected for family studies could additionally be used to better control for environmental exposures and to determine whether the pattern of disease within families is best explained by a single major gene, multiple genes, or shared environment. Further genetic analyses also include case-control studies that examine the association between ESRD and candidate genes hypothesized to play a role in the biological mechanisms leading to disease. Results from case-control studies looking at the association of candidate genes, such as the angiotensin-converting enzyme and type IV collagen α-1 chain genes, with increased risk of ESRD have not been consistent (27–32). The coordination of molecular and epidemiologic studies is needed to shed more light on the cause of ESRD and to facilitate the development of preventive strategies for high-risk individuals.

Acknowledgments

This work was supported in part by Swiss National Science Foundation Grant 32-32609.91. Dr. Lei was supported by National Institutes of Health Training Grant HL07024-22. Dr. Coresh is supported by FIRST award DK48362. Computational assistance was received

from National Institutes of Health General Clinical Research Centers Grants R00035 and R00072.

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