Kidney International, Vol. 67, Supplement 94 (2005), pp. S46–S49

Genetic factors in end-stage renal disease

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Genetic factors in end-stage renal disease. Despite more aggressive treatment of diabetes, hypertension, and hyperlipidemia, the incidence and prevalence rates of end-stage renal disease (ESRD) continue to increase worldwide. The likelihood of developing chronic kidney disease in an individual is determined by interactions between genes and the environment. Familial clustering of nephropathy has repeatedly been observed in all population groups studied and for multiple etiologies of kidney disease. A three- to nine-fold greater risk of ESRD is observed in individuals with a family history of ESRD. Marked racial variation in the familial aggregation of kidney disease exists, with high rates in African American, Native American, and Hispanic American families. Disparate etiologies of nephropathy aggregate within African American families, as well. These data have led several investigators to search for genes linked to diabetic and other forms of nephropathy. Evidence for linkage to kidney disease has been detected and replicated at several loci on chromosomes 3q (types 1 and 2 diabetic nephropathy), 10q (diabetic and nondiabetic kidney disease), and 18q (type 2 diabetic nephropathy). Multicenter consortia are currently recruiting large numbers of multiplex diabetic families with index cases having nephropathy for linkage and association analyses. In addition, large-scale screening studies are underway, with the goals of better defining the overall prevalence of chronic kidney disease, as well as educating the population about risk factors for nephropathy, including family history. Given the overwhelming burden of kidney disease worldwide, it is imperative that we develop a clearer understanding of the pathogenesis of nephropathy so that individuals at risk can be identified and treated at earlier, potentially reversible, stages of their illness.

End-stage renal disease (ESRD) has reached epidemic proportions, with more than 400,000 affected individuals in the United States, and well over one million worldwide. [1] These staggering numbers represent only the tip of the iceberg, as the incidence of chronic kidney disease is at least 30-fold higher than that of ESRD [2, 3]. At the current rate of growth, it is expected that the incidence rate of new ESRD cases in the U.S. will be over 400,000 *per year* in 2030, with an estimated prevalence of over two million [1]. The economic impact of this is staggering: the ESRD program in the U.S. in 2001 cost $22.83 billion [1]. This cost estimate includes only direct health care expenditures, and excludes indirect costs such as lost productivity. This has generated enormous interest in identifying risk factors for kidney failure, in the hope that earlier treatment can prevent ESRD from developing in susceptible individuals.

Enhanced susceptibility to chronic kidney disease can be caused by environmental factors, genes, and their interaction [4]. This review focuses on the association between genetic factors and ESRD, allowing that a permissive environment (i.e., hyperglycemia or hypertension) is required for expression of genetic susceptibility.

RISK ASSOCIATED WITH FAMILY HISTORY

One of the most important risk factors for developing chronic kidney disease in an individual is the presence of a family history of ESRD. Several U.S. reports reveal a three- to nine-fold greater risk of developing ESRD in individuals with relatives having ESRD [5–7]. Significant racial variation exists in susceptibility, with a high risk attributable to family history in the African American [8], Native American [9], and possibly Hispanic American [10] populations. In a case-control study from North Carolina, our group reported that African Americans with a first-degree relative on dialysis had a nine-fold higher risk of developing ESRD than did age-, sex-, and race-matched control subjects [6]. This association was also observed in African Americans residing in Los Angeles, where subjects with a history of chronic renal failure in first- or second-degree relatives had a greater than five-fold increased risk of ESRD compared with race-matched controls [5]. Our group found that family history also correlated with excess risk for ESRD in Caucasian Americans, albeit to a lesser extent. In this population, a three-fold higher risk was seen in individuals who had either first- or second-degree relatives with ESRD [7]. While racial predilections are seen, explanations for the racially variable susceptibility rates are not yet clear. It is likely that the increased familial clustering of chronic kidney disease in certain races is associated with genetic and environmental factors.

One's family history of ESRD is more predictive for subsequent development of chronic kidney disease in a hypertensive or diabetic individual than is the level of

Key words: genetics, end-stage renal disease, diabetic nephropathy.

blood pressure or glucose control [8, 11] This is not to suggest that control of modifiable factors such as hypertension and hyperglycemia does not play an important role in decreasing the likelihood of development or progression of nephropathy in susceptible individuals. Rather, it implies that individuals who are genetically susceptible to developing kidney disease need to pay even closer attention to modifiable risk factors.

Familial clustering of disparate causes of ESRD has been reported by several groups, including families with members having nephropathy associated with types 1 and 2 diabetes mellitus, hypertension, chronic glomerulonephritis, systemic lupus erythematosus, and human immunodeficiency virus (HIV) infection [6,12–16]. In addition, a case-control study by Lei et al concluded that familial clustering of renal disease occurred in excess of that which could be accounted for by the clustering of hypertension and diabetes mellitus within families [17]. Additionally, family history of hypertension or diabetes was not significantly associated with ESRD, once adjustment was made for personal history of these conditions. This suggests that additional factors beyond the presence of a permissive environment are necessary in order for nephropathy to develop.

Familial clustering occurs to a greater extent in members with early onset of nephropathy [8]. This has been observed in African Americans with HIV-associated nephropathy [14] and in Polish subjects with various etiologies of ESRD [18]. In this Polish population, early onset of ESRD (onset prior to age 45 vs. onset after age 65) was associated with a two-fold greater likelihood of a positive family history. A report from Lebanon found that 26% of 925 hemodialysis patients were offspring of consanguineous marriages [19]. Thirty-five percent of subjects from consanguineous marriages had early onset of ESRD (before age 30) compared with 21% of non-consanguineous offspring ($P < 0.01$). In this report, 6.2% of subjects had polycystic kidney disease, and 47% had undiagnosed etiologies of renal failure. However, the theme of these reports from diverse populations supports the concept that a genetic contribution to the familial clustering of renal disease exists.

In 324 patients from 80 families with autosomal-dominant polycystic kidney disease, the location of the PKD1 gene mutation correlated with both severity of renal disease and age at onset of ESRD [20]. Patients with PKD1 mutations in the 5′ region had a median age at ESRD onset of 53 years, while those with mutations in the 3′ region had median age at onset of 56 years ($P = 0.025$). Those individuals with 5′ mutations had only an 18.9% incidence of renal survival at age 60, compared with 39.7% of those with 3′ mutations. All subjects ($N = 6$) with onset of ESRD prior to age 35 had 5′ mutations. These findings were not replicated in a study in 461 patients from 74 families with PKD2 mutations [21]. In PKD2 families, the location of the mutation did not appear to impact age at onset of ESRD.

THE SEARCH FOR GENES ASSOCIATED WITH NEPHROPATHY

In the U.S., more than 35% of prevalent ESRD patients have diabetic nephropathy. It is anticipated that as many as 58% will have diabetes-associated ESRD in 2030 [1]. Due to the substantial health care burden of diabetic ESRD and the marked familial aggregation, this population has been targeted for genetic analysis.

A major susceptibility locus for type 1 diabetic nephropathy was identified on chromosome 3q using discordant sib-pair analysis. Sixty-six Caucasian American siblings concordant for type 1 diabetes mellitus, but discordant for renal disease, were evaluated [22]. This putative diabetic nephropathy susceptibility locus lies within a 20-cM region surrounding the angiotensin II type 1 receptor gene (ATI). Confirmation of linkage in type 1 diabetic nephropathy was provided in ethnic Russians on chromosome 3q21-25, in the vicinity of the ATI gene [23].

We performed a genome-wide scan in 206 sibling pairs concordant for type 2 diabetic nephropathy from 166 African American families. Ordered subsets analysis (OSA) and nonparametric linkage (NPL) regression analysis demonstrated consistent evidence for linkage on chromosomes 3q, 10q, and 18q [24]. The 3q peak was in the same region as the type 1 diabetic nephropathy locus reported by Moczulski et al [22] and Savost'ianov et al [23].

In Caucasian Americans with type 2 diabetes mellitus (662 subjects from 310 families, with 422 diabetes-concordant sib pairs), the estimated heritability (h^2) of glomerular filtration rate (GFR) was 0.75 ± 0.10 ($P < 0.0001$) after adjustment for age, sex, mean arterial pressure, medications, and hemoglobin A1c [25]. Heritability of urine albumin-creatinine ratio (ACR) was 0.46 ± 0.12 ($P < 0.0001$) after similar adjustment. These covariates were estimated to account for only 2% of the total phenotypic variance in log GFR and 9% of the total phenotypic variance in ACR.

In an attempt to assess for linkage between markers on human chromosome 10 [in the region of the human homologue of the rodent renal failure 1 gene (*Rf*-1)] and ESRD, we performed a linkage analysis in 356 African American sib-pairs concordant for ESRD (with etiologies including hypertension, diabetes mellitus, glomerulonephritis, or unknown cause of ESRD) [26]. In African American individuals with early onset, nondiabetic etiologies of ESRD, suggestive evidence for linkage was identified on chromosome 10p, near marker D10S1435, and this has been confirmed in diabetic families as well [27]. Variation in creatinine clearance in European

Americans with essential hypertension has also been linked to markers on chromosome 10 [28].

The Family Investigation of Nephropathy and Diabetes (FIND) is a multicenter, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored consortium which is currently performing family-based linkage analyses on diabetic sibs both concordant (affected sib pairs, ASPs) and discordant (discordant sib pairs, DSPs) for nephropathy [29]. Recruitment of nearly 10,000 subjects has been anticipated by late 2004. In addition to family-based linkage analyses in African American, American Indian, Hispanic American, and European American sibs, mapping by admixture linkage disequilibrium (MALD) analyses are being performed in unrelated African American and Hispanic American diabetic nephropathy cases and diabetic non-nephropathy controls. The Genetics of Kidney Disease in Diabetes (GOKIND) study is in the process of recruiting a planned total of 1100 trios of type 1 diabetic individuals (with and without nephropathy) and their parents for transmission disequilibrium testing [30]. Both of these large-scale studies have the ultimate goal of identifying the causative genes linked to diabetic nephropathy.

POPULATION-BASED SCREENING STUDIES

More than 35,000 incident dialysis patients were enrolled in the U.S. ESRD Network 6 "Family History of ESRD" registry. A pilot study from our institution attempted to contact first-degree relatives of a random sample of ESRD index cases from this registry [31]. Relatives were encouraged to visit their primary care physicians for renal-related health care screening. Among 88 relatives, a significant number were found to have risk factors for kidney disease, although none had renal insufficiency. Nearly 22% of relatives had uncontrolled hypertension, 18.1% elevated fasting serum glucose, and 26.2% albuminuria. The second phase of this study will involve a health-fair type screening of a larger number of first-degree relatives from index cases at multiple dialysis units in North Carolina.

The National Kidney Foundation's Kidney Early Evaluation Program (KEEP) has conducted community screening of high-risk individuals throughout the United States since 1997 [32, 33]. High-risk individuals include those with a personal history of diabetes or hypertension, and those with a family history of diabetes, hypertension, or chronic kidney disease in a first-degree relative. To date, over 11,000 subjects have undergone screening [33]. During the first year of screening in 889 subjects, 420 had laboratory abnormalities suggestive of nephropathy (114 with elevated serum creatinine concentration, 170 with microalbuminuria, 137 with pyuria, and 165 with hematuria) [32]. In both the "Family History of ESRD" and KEEP screening studies, many individuals with evidence of either nephropathy or risk factors for nephropathy were previously unaware of their status.

The largest such screening study reported to date has been carried out by the National Kidney Foundation of Singapore, enrolling 213,873 adults of Chinese, Malay, and Asian Indian descent [34]. In contrast to the two U.S. screening studies, the Singapore study enrolled healthy adults at their work sites, rather than targeting high-risk individuals. Complete data regarding family history of kidney disease was obtained for 158,576 subjects, 5893 of whom (3.7%) reported a positive history. It is not clear what percentage of subjects had relatives with ESRD, or what percentage had first-degree relatives (as opposed to distant relatives) with nephropathy. Multivariate analysis revealed a highly significant association between family history of kidney disease and personal history of proteinuria (odds ratio 2.0, $P < 0.001$). This study contains valuable information, as most of the prior epidemiologic data regarding family history of nephropathy have been reported in populations of European or African descent.

CONCLUSION

Considerable evidence supports family history of renal disease as one of the most important risk factors associated with development of nephropathy. The familial clustering of ESRD supports a genetic contribution to the pathogenesis of chronic kidney failure. Genomic analyses and family-based screening studies are underway to more clearly define the role of genomic factors in nephropathy susceptibility. Identification of causative genes may allow the development of novel therapies targeted at gene products. Hopefully, these therapies will delay or prevent progression of chronic kidney disease and curb the worldwide epidemic of ESRD.

ACKNOWLEDGMENTS

This work was supported, in part, by National Institutes of Health grant RO1-HL56266 (B.I.F.). The authors are grateful to Mrs. Kim Hairston and Mrs. Laura Furr for their secretarial assistance.

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