

RENAL DISEASE: ENVIRONMENT, RACE, OR GENES?

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Diabetic nephropathy is over-represented in people of color. This reflects both environmental and genetic factors. Numerous studies assess the effects of access to care and patient adherence in the development of kidney diseases. After correcting for these factors, genetic influences remain. Genetic approaches to discerning genes that predispose to diabetic nephropathy include candidate gene approaches, linkage analysis, mapping by admixture linkage disequilibrium, and transmission disequilibrium testing. Numerous candidate genes have been identified, although few have been confirmed apart from those representing genes in the renin-angiotensin system. The results of linkage analysis studies have similarly resulted in genomic regions purported to show linkage in a variety of ethnic groups that have most often not been confirmed in other ethnic groups, and sometimes in other groups of similar ethnicity but different phenotype definitions. The chromosomal regions determining glomerular filtration rate do not appear to be localized to the same chromosome as those related to proteinuria. Large cohorts of subjects have now been amassed by numerous research groups, and genome-wide scanning results involving much larger cohorts are anticipated to be published in the next few years. It is hoped that these strategies will ultimately identify chromosomal regions and/or genes that confer risk for diabetic nephropathy, and in so doing, provide clues to new therapies. (*Ethn Dis.* 2006;16 [suppl 2]:S2-35–S2-39)

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This review will address the contributions of ethnicity, race, and genetic predisposition to the development and progression of renal disease. A recent report by the Agency for Health Care Research and Quality in the United States suggests that disparities exist in the US healthcare system. The draft submission said that racial, ethnic, and socioeconomic disparities are national problems that affect health care at all points in the process, at all sites of care, and for all medical conditions. In fact, disparities in the healthcare system are pervasive. However, as released, this study said, “This report finds that while most Americans receive exceptional quality of health care and have excellent access to needed services, some socioeconomic, racial, and ethnic differences still exist.”¹ The bottom line is that disparities in health care are still prevalent in the United States, and this fact is highlighted in the incidence and prevalence of many of the underlying causes of chronic kidney disease (CKD).

End-stage renal disease (ESRD) is the most severe stage of CKD and disproportionately affects people of color. Data from the United States Renal Data System (USRDS) show that the prevalent rates for White patients have been low and relatively stable over the last eight years, whereas for Black Americans and Native Americans, the rate of ESRD is considerably higher. Trends in incident rates of ESRD are also increasing at higher rates for Native Americans and African Americans compared to Asians and Whites.²

Access to care and counseling is also uneven. Access is poor for all ethnic groups. However, the Indian Health Service is doing better in this regard

than most other providers of care. Nevertheless, despite overall poor access to care and counseling among non-Native American groups, the provision of these elements is slightly better for Whites than for people of color.²

Compliance to appointment schedules and treatment regimens are different in people of color than in Whites in the United States.^{3–5} The Insulin Resistance in Atherosclerosis Study showed that African Americans were more likely to have poorly controlled diabetes, and both African Americans and Hispanics are more likely to have borderline or poorly controlled hypertension than non-Hispanic Whites.³ To minimize the impact of access to care, studies to measure compliance were performed in settings like urban managed care organizations. In one such study, African Americans with diabetes were less likely than Whites to undergo routine primary care visits and laboratory testing and were more likely to have suboptimal glycemic control.⁴ In The Atherosclerosis Risk in Communities (ARIC) study, 80% of the threefold risk for declining renal function in African Americans with diabetes was due to modifiable factors.⁵ In some sense, that news is good because we can address those issues, which included low socioeconomic status, poor blood pressure and glycemic control, and other suboptimal health behaviors, the most important of which was smoking.⁵

Different co-morbidities are seen across ethnicities in patients with diabetic nephropathy. For instance, hypertension is more prevalent in dialysis patients who are African American. In addition, diabetes is over-expressed in Native Americans compared to other

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ethnic groups, and congestive heart failure (CHF) tends to be somewhat more frequent in White patients than in Blacks or Native Americans.² Members of different ethnic groups may respond to specific drugs differently. A report by Exner et al suggested that enalapril in comparison to placebo was effective in reducing rates of hospitalization for CHF in Whites but less so in Blacks, and then only after very long-term follow-up.⁶

Differences in outcomes are not always what one would anticipate. In ESRD patients, all-cause mortality is much higher in White patients than it is in Asians, African Americans, or Native Americans, and cardiovascular mortality is also higher in the White population than in other groups. This is a consistent finding from the USRDS, so risk factors that affect people of color do not always correlate with worse outcomes in selected settings.² These differences represent the effects of an amalgam of causality-related environmental and genetically conferred risk, reverse epidemiology of CV risk factors in ESRD, and/or other factors.^{2,7}

The strongest environmental association for the remission or progression of renal disease is for glucose with diabetic nephropathy. It is the perfect "wedding" of biologic plausibility and clinical confirmation. Glucose, in the presence of hyperlipidemia and systemic and intraglomerular hypertension, induces a number of pathogenic processes that lead to both the histologic and clinical manifestations of diabetic kidney disease. Given that pathophysiology, one can see that if glucose is controlled, as was done in the Diabetes Control and Complications Trial (DCCT) for patients with type 1 diabetes, microalbuminuria is reduced by 39% and overt proteinuria by 54%, thus demonstrating that the incidence of the disease phenotype can be diminished by altering the (glycemic) environment.⁸ Similar results were obtained in the United Kingdom Prospective

Diabetes Study Group (UKPDS) study of type 2 diabetes.⁹ As hemoglobin A1C is reduced, microvascular endpoints are diminished.⁹ The DCCT study also shows that for every 1 percentage point improvement in hemoglobin A1C, microvascular endpoints decline by 37%.⁸

Controlling blood pressure is another modifiable element. The UKPDS showed that as systolic blood pressure is lowered, microvascular endpoints and myocardial infarction rates diminish.¹⁰ Of course, specific antihypertensive agents confer differential benefits in the prevention of microvascular and macrovascular disease. Studies to demonstrate this fact, for renal disease specifically, include the Angiotensin Converting Enzyme Inhibition with Captopril in Diabetic Nephropathy study, Irbesartan in Diabetic Nephropathy Trial, and the Reduction in Endpoints of NIDDM with the Angiotensin II Antagonist Losartan study.¹¹⁻¹⁴

Thus, the rule is that in diabetes, environmental modification (treatment) alters the initiation and progression of renal disease. The corollary to this rule is that adequate access to care is needed to prevent and delay illness and death. For nondiabetic renal disease, environmental associations are not nearly as tightly related. For instance, a study from the Hopkins epidemiology group showed that acetaminophen may increase the risk of progression to ESRD if CKD is already present.¹⁵ Whether this epidemiologic association has biologic relevance is unclear. Similarly, cigarette smoking has been suggested as a formidable risk factor for progression. In one study, a history of smoking increased the risk of CKD at each stage of hypertension.¹⁶ Other modifiable environmental factors may contribute to initiation or progression, including diet, body weight, and physical activity; whether or not insulin or peroxisome proliferator-activated receptor agents are used; and exposure to other medications or toxins, lead, Chinese herbs,

and alcohol. Numerous environmental factors contribute to the initiation or progression of nephropathy.¹⁷ Despite a clear role for environmental factors in the initiation and progression of nephropathy, clinical observations of disease in the apparent absence of environmental contributions suggests genetic contributions. Furthermore, the paradox of high cardiovascular mortality (eg, in White patients with ESRD) despite fewer risk factors also suggests something besides environmental factors determines risk.

Most nephrologists have encountered families in which the ravages of diabetes are disproportionately expressed. Clustering of diabetic complications is well known¹⁸ and exemplified in one closely followed proband at our center who had diabetes for 11 years and had cardiovascular disease, nephropathy, peripheral vascular disease, and retinopathy, with similar complications among the siblings, parents, and grandparents. The pattern appears to be genetic, although we cannot exclude an environmental contribution.¹⁹ Through a reduction to the simplest experiment, we can demonstrate a relationship between glycemia and diabetic complications. In an elegant yet simple genetic model of how genes can affect a response to glycemia by Charles Helig and colleagues, mesangial cells were cultured in normal glucose, and they were shown to synthesize a certain amount of collagen. However, when those mesangial cells were placed into high-glucose medium, they "behaved" diabetic; that is, they made more collagen. If mesangial cells were then genetically modified so that the number of Glut 1 transporters on the surface was increased and they were placed into a normal-glucose environment, they synthesized even more collagen.¹⁹

The evidence for genetic predisposition in diabetes is numerous.²⁰⁻²⁶ Diabetes risk clusters in families, and the magnitude of that increased risk varies according to ethnicity. For instance, in

European-Americans with type 1 diabetes, the lifetime risk is 33%, but the incidence peaks at the second decade and declines afterwards, suggesting depletion of a susceptible population.²⁷ Furthermore, the diabetic sibling of a person who has diabetes and nephropathy is twice as likely to develop nephropathy as is a diabetic sibling of a diabetic without nephropathy.²⁷ Mice have specific renal failure genes that confer risk to nephropathy.²⁸ In some ethnic populations, the homologs of mouse risk genes have been identified as potential risk factors for diabetic nephropathy. Freedman et al, in a linkage analysis study, suggests that ESRD links to the RF1 mouse risk gene in African Americans.²⁹ Iyengar et al published linkage at close to, but distinct from, RF1 and a smaller peak at RF1 in European-American subjects with diabetic nephropathy and ESRD.³⁰ Nephropathy risk can actually be transferred by the RF1 gene, reaffirming that genetics plays a role.²⁸ Evidence for heritability of specific renal manifestations in humans is also seen.³¹⁻³⁵ Among siblings, Fioretto et al showed strong concordance for mesangial fractional volume, mesangial cellularity, and mesangial matrix fractional volume.³⁶ Clustering of similar glomerular lesions tended to be concordant when examining the degree of mesangial expansion or glomerular basement membrane thickening among siblings.³⁶ The Framingham Heart Study also showed genetic control for nephropathy. Heritability for serum creatinine, creatinine decrease, and glomerular filtration rate were estimated as 0.29, 0.33, and 0.46, respectively. Linkage peaks were identified at sites on chromosomes 3, 4, and 11.³⁷

Candidate gene studies have identified numerous genes that may confer diabetic nephropathy risk, and methods for identifying risk genes have been reviewed.³⁸ In general, these candidate genes can be classified as those that involve the renin-angiotensin system,

extra cellular matrix, growth factors, or signaling and transcription or miscellaneous genes. The importance of the renin-angiotensin system is supported by meta-analyses.³⁹⁻⁴⁰ Approximately 30%–40% of the risk of diabetic nephropathy has been estimated to be due to angiotensin-converting enzyme polymorphisms.⁴⁰ The problem with most candidate gene studies is the lack of consistency. On the one hand the lack of emergence of a small number of genes with great effect, despite prodigious efforts to define them, may be explained by experimental artifact, random events, or false-positive results. Alternatively, discordance in the candidate gene studies may reflect heterogeneity from small effects in a large number of genes in studies with variable power to detect them and/or ethnicity-specific effects of some genes.

Thus, the incongruities of genetic studies across ethnicity raise the question of whether race and ethnicity are relevant or whether they are linked to genetic influences on nephropathy. Ethnicity denotes cultural differences. Race is poorly defined. The popular meaning of race has to do with skin color and other phenotypic differences. However, geneticists do not mean skin color when they say race. They define race as denoting the geographic origin of an individual's ancestors. In the genetic sense, race refers to continent of origin. Essentially 5 races are defined: Africans, Caucasians, Pacific Islanders, east Asians and Native Americans.⁴¹ In a study of 14 indigenous populations from five continents, these populations cluster into five continental groups when examined with just 30 microsatellite loci.⁴²

However, migration blurs the preservation of race defined by continental boundaries.⁴³ Thus, surprising genetic groupings of race are found, particularly among Caucasians, who by this kind of characterization are actually composed of people from Europe, west Asia, the Indian subcontinent, the Middle East,

and North Africa.⁴³ This classification is quite different than defining race by skin color. Therefore, because of this migrational effect, epidemiologists use tools to try to disentangle environment from genetic influence. These tools include migrant studies, stratified analyses, and disequilibrium mixture, which is a correlation of individual admixture at specific locations in the genome for a given trait.

Sensitivities regarding race have introduced conflict between actual scientific data and the politics of political correctness. The *New England Journal of Medicine* responded in a paper called "Race Profiling in Medical Research" that race is biologically meaningless and that instruction in medical genetics should emphasize the fallacy of race as a scientific concept and the dangers inherent in practicing race-based medicine.⁴⁴ It has been estimated, only partly in jest, that genetically humans are 50% identical to bananas and 99.9% identical to each other. However, in genetic studies intended to find disease risk genes, geneticists look for differences in the tiny fraction of human genes that are different from each other. Insisting on a color-blind or a race-blind paradigm that naively argues against differences limits scientific inquiry. Science suggests an alternative paradigm in which humans are a little bit different one from another, sometimes in important ways. Thus, searching for genetic risk in complex genetic diseases is easier among subjects of similar race and ethnicity because of the different frequencies of polymorphisms that are observed in different groups. In a recently published study, genetic cluster analysis correlated well with self-identified race and ethnicity among subjects of European, African American, east Asian and Hispanic origins, arguing that genetic veracity or consistency exists in the concept of race.⁴⁵

How well have we done in finding genes among different ethnic groups in

complex disorders? Genome-wide linkage studies have been discordant. In Pima Indians, linkage was identified at peaks on chromosomes 3, 7, 9, and 20.⁴⁶ In Caucasians, linkage was identified, but the locus on chromosome 3 does not overlap with that identified in Pimas, and is not proximate to the AT1 receptor.⁴⁷ In African Americans, linkage peaks on chromosome 12 and 20 have been identified.⁴⁸ Finally, in European Americans, linkage peaks were reported on chromosome 10.³⁰ In a preliminary report from the Family Investigation of Nephropathy of Diabetes study, diabetic nephropathy linkage peaks on chromosome 7 and 8 were associated with albuminuria/proteinuria and estimated glomerular filtration rate across ethnicities,^{49,50} but many other chromosomal loci appeared to be ethnicity-specific. Thus, ethnicity seems to play a role in disease risk.

To summarize, ethnicity and race appear to play roles in the development of some complex disorders such as diabetic nephropathy above and beyond the effects of environmental influences. These differences may be capitalized upon to define risk and discover therapies.

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AUTHOR CONTRIBUTIONS

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