expressed in lengthened cilia as a result of Nek8 mutations (NPHP9) speaks to the same mechanism as a disease in which polycystins are nonfunctional or absent from cilia (ADPKD). It remains possible that the observed alterations in polycystin protein in cilia are the result of a more generalized alteration in cilia composition, and if one looked at a spectrum of cilia proteins, then a generalized abnormality not restricted to polycystins may be observed. It is important in studying cilia-related structural diseases of the kidney that we continue to seek unbiased approaches toward understanding mechanism and remain cautious in focusing only on what we know. This was a lesson well learned once before in this field when cilia were unknown in cystic disease and may yet be the lesson for the future as well.

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DISCLOSURES

None.

REFERENCES


Naturally Too Sympathetic to a Bad Diet?

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An ominous upward trend in obesity, diabetes, and associated hypertension and their consequences warns all of us of a burden in cardiovascular disease already well developed in the United States and sweeping across Europe, many parts of Asia, and beyond. It seems set to get worse. This epidemic includes an alarming rise in chronic renal failure reaching ESRD and requiring long-term dialysis or transplantation. In the United States, this rose from approximately 42,000 in 1978 to >484,000 by 2005 (11.5-fold).1 Black individuals of

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ancestral African descent are disproportionately susceptible to renal damage developing in this epidemic having particularly high rates of ESRD associated with hypertension. Reported prevalence rate of ESRD in black individuals is >2.5-fold the US population average.1

Within this population are clear genetic factors causing susceptibility. In a small minority (8%) these are single-gene disorders, such as FSGS from mutations in genes encoding ACTN4, TRPC6, or CD2AP (FSGS1 through 3), and give insight into how susceptibility develops.2 However the majority seem cases of a complex polygenic disorder: arising as ancestral genotypes, adapted to hunter-gatherer sub-Saharan lifestyle, interact with the modern, increasingly Westernized environment and a sedentary lifestyle. Diet has loomed large among environmental culprits. Presuming ancestral diets were low calorie and low sodium, selection would favor genotypes enabling increasing food intake and putting on weight when calories are available and retaining salt avidly, suiting a low-salt diet. On exposure to this Westernized lifestyle, these survival traits then predispose to obesity, diabetes, and hypertension. ESRD seems to be a particular vulnerability with nondiabetic ESRD usually attributed to hypertensive nephrosclerosis.

Understanding this genetic susceptibility of black individuals to ESRD is of great interest, and many candidate genes have been proposed and investigated, especially in pathways relating to renal damage or other renal structural diseases, such as TRPC6 (FSGS-2) or podocin (steroid-resistant nephrotic syndrome).3 Increasingly in this post-genomic, post-HapMap era, the rigor of candidate gene reports warrants serious consideration. In this issue of JASN, Salem et al4 report that variations in chromogranin A (CHGA) genotype are associated with ESRD in hypertensive black individuals versus control subjects with normal renal function and hypertension or normotension. Multiple single-nucleotide polymorphisms (SNP) analyzed in a Californian cohort across the CHGA locus identify significant associations with a three-SNP proximal promoter haplotype and a 3’end/3’untranslated region two-SNP haplotype.

Importantly, findings in a second, unrelated cohort of black individuals from North Carolina validated significant associations of ESRD with both haplotypes (both emerging as two-SNP haplotypes). In both haplotype regions variation has potential to alter CHGA expression4,5 with the 3’haploype 87T SNP allele reducing expression by >40%.4 Consistent with such haplotype effects to lower gene transcription, circulating levels of catestatin (a chromogranin A cleavage product) were significantly reduced in patients with ESRD versus control subjects despite the tendency for accumulation in ESRD. Because catestatin is active in limiting catecholamine release, these findings suggest the ESRD-associated haplotypes would leave the sympathetic nervous system (SNS) less restrained, implying that relative SNS overactivity is pathophysiologically involved in the susceptibility to renal decline.

Could catecholamine release and sympathetic overactivity really be key processes underpinning hypertensive renal damage and ESRD in black individuals? The suggestion certainly has potential to arouse skepticism. Although antihypertensive drug classes in use decades ago included a group limiting SNS activity (ganglion blockers, adrenergic α2 agonists [e.g., clonidine], α-methyl DOPA, and β blockers), it was not these but diuretics that emerged as particularly valuable in treating hypertension and its consequences in black individuals.

Such hypertension is indeed salt sensitive, and guidance favoring diuretics remains in many current guidelines on treatment of hypertension.6,7 However it is important to appreciate that the association with chromogranin A is not with hypertension but renal damage, potentially largely independent of systemic hypertension. Indeed, in the important African American Study of Kidney Disease and Hypertension (AASK), factors other than systemic BP (mainly proteinuria) and drugs other than diuretics emerged as key in limiting decline in renal function.8 That angiotensin-converting enzyme inhibitors (ACEI) were best and β blockers probably worst at limiting renal damage also seems to give little support to the role of sympathetic overactivity in these processes. However, dysregulation of glomerular hemodynamics leading to glomerular hypertension-driven proteinuria seem to be involved and ameliorated by ACEI. It is possible that the wrong balance of α and β adrenergic overactivity could promote dysregulation of glomerular hemodynamics and not be optimally resolved by β blockade. α Blockers certainly can alter glomerular pressure, and studies showing combined α and β blockade ameliorating renal damage and proteinuria in animals are known.9 More intriguing still, there are 6 α adrenoceptors (fully selective blockers are not available), and, in mice, null alleles of α1a10 or α1d11 lower and α2a12 raise BP, and these along with α2b13 are implicated in separate chronic salt-sensitive SNS responses and BP abnormalities.

Because high-salt intake, obesity, and uremia all are associated with SNS overactivity, it is clear that abnormalities in selective α adrenoceptor pathways might be a route through which sympathetic overactivity promotes salt-sensitive hypertension and simultaneous vulnerability to renal damage. Finally, chromogranin A haplotypes (and perhaps reduced circulating catestatin) are potentially valuable markers in identifying a subset of people who may benefit from specific treatment to avoid ESRD (for example, ACEI) at an early stage: rather like impaired glucose tolerance (another marker of the Western-lifestyle epidemic), warrants assessment of need for such treatment.

This report is rigorous in validating initial haplotype findings in a second population, although the studies presented nonetheless have weaknesses (e.g., sympathetic tone changes with age and control subjects are an average 10 yr younger). It seems that further study is warranted for both this interesting
candidate gene and the theory that sympathetic overactivity is an underestimated contributor to ESRD.

Although considerable further evidence would need to follow to verify the putative causal chain, ideally early developments would be that others would reproduce the findings in larger populations, and longitudinal studies in patient groups or animal models would demonstrate that sympathetic overactivity (and lower catestatin) precedes progressive decline to renal failure. Eventually, then, the value of these CHGA haplotypes and catestatin as markers and perhaps the benefits of medication that is capable of limiting the distorted sympathectic outflow, perhaps limiting certain an adrenergic effects, might then be worth assessment in those who are at high risk for ESRD.

DISCLOSURES

None.

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See related article, “Chromogranin A Polymorphisms Are Associated with Hypertensive Renal Disease,” on pages 600–614.

Author Misrepresentation in the Submission of Redundant Papers

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When are two original papers by the same authors redundant? Variations in study design around similar themes might enable plausible claims of distinction, but the average reader can quickly perceive commonality and overlap. Authors use all or part of the same data set, come to similar conclusions that have no incremental value, produce overlapping communications that could easily have been distilled to one, and waste the time of our reviewers and readers. Redundant publications also deprive other authors of space to have their own articles chosen for print in well-regarded journals. This is annoying and usually caught during the review process, except when it is not disclosed.

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