see clinical investigation on page 114

Hypertension-misattributed kidney disease in African Americans

Karl L. Skorecki[1] and Walter G. Wasser[2]

Lipkowitz *et al.* extend the African American Study of Kidney Disease and Hypertension to the level of genetic epidemiology, in a case–control study design. Analysis of genotypes at the *APOL1* kidney disease risk region supports a paradigm shift in which genetic risk is proximate to both kidney disease and hypertension. The findings mandate urgency in clarifying mechanisms whereby *APOL1* region risk variants interact with environmental triggers to cause progressive kidney disease accompanied by dangerous hypertension.

Kidney International (2012) **83,** 6–9. doi:10.1038/ki.2012.369

Nephrologists in North America have long observed that African Americans with hypertension-associated kidney disease display a poor kidney-protective response to medications that effectively lower arterial blood pressure and a more rapid pattern of kidney disease progression compared with their non-African counterparts. The chicken-and-egg conundrum of hypertension as a cause of nondiabetic, secondary kidney disease or a consequence of primary kidney disease was effectively addressed by the findings of the African American Study of Kidney Disease and Hypertension (AASK) trial and cohort follow-up studies.[1] African-ancestry participants in this landmark comparative therapeutic intervention trial, receiving antihypertensive agents, including angiotensin-converting enzyme inhibitors, appeared not to accrue the benefit expected from effective control of systemic arterial blood pressure, in terms of progression to end points indicative of chronic kidney disease.[1] (A subgroup of subjects with urine protein-to-creatinine-excretion ratios greater than 0.22 g may have shown relative benefit from angiotensin-converting enzyme inhibitor therapy.) Although not directly comparable, observational studies in population groups without sufficient representation of people of recent African ancestry supported the conventional wisdom of a kidney-protective benefit from antihypertensive therapy, even in nondiabetic kidney disease.[2] In contrast, the AASK studies strongly suggest that an underlying factor(s) other than hypertension per se might be responsible for chronic kidney disease risk with hypertension as an accompaniment, at least among African Americans. The epidemiologic inference is further strengthened by the strikingly different histopathology in the kidneys of African- versus non-African-ancestry people clinically labeled with 'hypertensive nephrosclerosis.'[3] The foregoing would not be expected if a single disease entity were present.

Lipkowitz and colleagues[4] (this issue) now provide elegant further resolution at the molecular epidemiologic level, by relating the AASK findings to the rapidly evolving story of powerful kidney disease risk variants at a chromosome 22q genomic region containing the genes *MYH9* and *APOL1*. Although some questions remain about the former, the finding of an association of two DNA sequence risk variants (designated as the G1 and G2 alleles) at the *APOL1* gene with certain major forms of nondiabetic kidney disease has transformed our understanding of population ancestry disparities in kidney disease risk.[5–7] Evolutionary adaptive pressures related to a past survival advantage in the face of a potentially lethal pathogen (*Trypanosoma brucei rhodesiense*) have resulted in the rise to high frequency of these two *APOL1* alleles in the parental populations of people from many regions of sub-Saharan Africa. Unfortunately, these same alleles are strongly associated with kidney disease. Thus, for example, the overall risk of developing nondiabetic end-stage kidney disease not attributable to known mendelian genetic or anatomic kidney disease may be increased more than threefold in the presence of two risk alleles.[7] Furthermore, even the presence of one G1 risk allele may accelerate the onset of end-stage kidney disease.[8–10] Among the etiologic entities that contribute the highest odds ratios (ORs) are HIV-associated nephropathy (OR, 29; 95% confidence interval (CI), 13–68) and primary non-monogenic focal segmental glomerulosclerosis (OR, 17; 95% CI, 11–26),[9] both diseases generally characterized by marked glomerular-range proteinuria. Clearly the vast majority of progressive nondiabetic chronic kidney disease in African Americans does not fit either of these latter two classical etiologic presentations, and is often accompanied by hypertension with no proteinuria or only low-grade proteinuria. In these cases, the default diagnosis had been 'hypertensive nephrosclerosis,' comprising more than 35% of the etiologic category in the US Renal Data System end-stage kidney disease registry for African Americans.[11]

[1]*Rappaport Faculty of Medicine and Research Institute, Technion–Israel Institute of Technology, Rambam Health Care Campus, Haifa, Israel and* [2]*Rambam Health Care Campus, Haifa, Israel*
Correspondence: *Karl L. Skorecki, Rappaport Faculty of Medicine and Research Institute, Efron Street, Technion–Israel Institute of Technology, Rambam Health Care Campus, Haifa 31096, Israel. E-mail: skorecki@tx.technion.ac.il*

A major conceptual transformation with important further practical implications is now clearly in order in light of Lipkowitz *et al.*'s insightful and informative population genetic and case–control addition to the AASK trials. Lipkowitz *et al.*[4] report the G1 and G2 allelic state (as well as genotypes of several other sites in the region and at informative genome-wide ancestry markers) in 675 AASK cases and 618 non-nephropathic controls. The cases were African Americans recruited throughout the United States, between the ages of 18 and 70 years with diastolic blood pressure higher than 95 mm Hg and a measured iothalamate glomerular filtration rate between 20 and 65 ml/min/1.78 m^2, indicative of chronic kidney disease. Since non-nephropathic controls were not part of the AASK cohort, these African-American subjects were recruited at Wake Forest School of Medicine and fulfilled the enrollment criteria of serum creatinine concentrations less than 1.5 mg/dl in men and less than 1.3 mg/dl in women.

Case–control analysis showed a highly significant association of the G1 genotype and the AASK label of 'hypertensive nephropathy' under a recessive inheritance model. While ORs are higher in HIV-associated nephropathy and focal segmental glomerulosclerosis as noted above, the finding of an OR of 2.57 (95% CI, 1.85–3.55), with $P = 1.4^{-8}$ despite the relatively small sample size, can be considered a vindication of the currently much maligned 'common disease, common variant' formulation. The clinical phenotype of hypertension with chronic kidney disease affects millions worldwide, and the associated G1 allele frequencies are well into the 'common' range in the population of interest (51% of African Americans carry at least one risk allele[7]). The association of *APOL1* G1 was stronger still with more advanced kidney disease at AASK baseline (urine protein-to-creatinine-excretion ratio >0.6 g/g) (OR, 6.29; 95% CI, 3.92–10.11; $P = 2.6^{-14}$), and with serum creatinine greater than 3 mg/dl during follow-up (OR, 4.61; 95% CI, 3.14–6.76; $P = 5.6^{-15}$). As in previous studies, associations with the lower-frequency G2 risk allele were more difficult to prove—perhaps for statistical or possibly biological reasons.[8,9]

Lipkowitz *et al.*[4] took full advantage of the treatment arms of the original AASK intervention trial, which used a two-by-three factorial design to examine the effects of medication class (calcium blocker, angiotensin-converting enzyme inhibitor, and beta-blocker), and of intensity of blood pressure control ('usual,' mean arterial pressure $<$102–107 mm Hg, versus 'low,' mean arterial pressure $<$92). Importantly, there was no observable influence of *APOL1* genotype on achieved blood pressure in the usual- and low-intensity arms. Disappointingly perhaps, multiple analyses, including a general linear model, did not demonstrate a significant interaction of age- and sex-adjusted medication-class group, nor of intensity of blood pressure control arm, with the *APOL1* allelic state, under a recessive model. In other words, in contrast to conclusions from recent kidney graft survival studies,[12] African-ancestry people with no *APOL1* risk variants cannot yet be approached with treatment paradigms that seem to apply to non-African-ancestry counterparts. Although the relative benefit reported for angiotensin-converting enzyme inhibitors in the original non-genotyped AASK trial and cohort studies for proteinuric subjects (protein-to-creatinine ratio >0.22 g/g) was not replicated in the current study, it may be premature to dismiss a role for *APOL1* genotyping in guiding antihypertensive medication choice and usage in African-ancestry populations. It should also be kept in mind that in the AASK trial, patients with low levels of proteinuria who were randomly assigned to the low blood pressure group, experienced worse outcomes compared to the usual blood pressure group.[13]

The study by Lipkowitz *et al.*[4] also made a valiant attempt to address the crucial question of whether or not hypertension, in the absence of clinically overt kidney disease, may also be associated with the *APOL1* kidney disease risk region. The investigators were able to question 409 of the 618 controls, and among these, 171 (41.7%) recalled having been told of hypertension by their health-care professionals or reported using antihypertensive medication. In particular, comparison of subsets of controls phenotyped in this manner for hypertension status showed no relation to *APOL1* genotype. This provides a tentative suggestion that hypertension in the absence of chronic kidney disease in African Americans may not be related to a clinical entity of subclinical *APOL1* associated kidney disease. However, an important caveat is the possibility that in the absence of kidney biopsy, large numbers of people might exist with subclinical forms of *APOL1*-associated primary kidney disease with hypertension as a first clinical manifestation. Since it is unlikely that kidney biopsies would be performed, an appropriate clinical study should be designed to address this question. This new study should include large numbers of participants with careful and objective determination of blood pressure status, no other evidence of kidney disease at enrollment, and long-term follow-up with tailored examination of the benefit of the antihypertensive therapy conditioned to *APOL1* genotype in the African-ancestry population.

Perhaps the most appropriate venue for such a study is the African continent, where appreciation of hypertension accompanied by life-threatening complications is growing, and progressive chronic kidney disease without recourse to kidney replacement therapy is the rule (Figure 1). Keeping in mind the need to effectively treat hypertension to prevent nonrenal complications as well, in such a setting it becomes mandatory to have a comprehensive understanding of the possible kidney origin of hypertension (including *APOL1* risk allele nephropathy), and the relationship between preferred modalities of treatment for hypertension and preservation of kidney

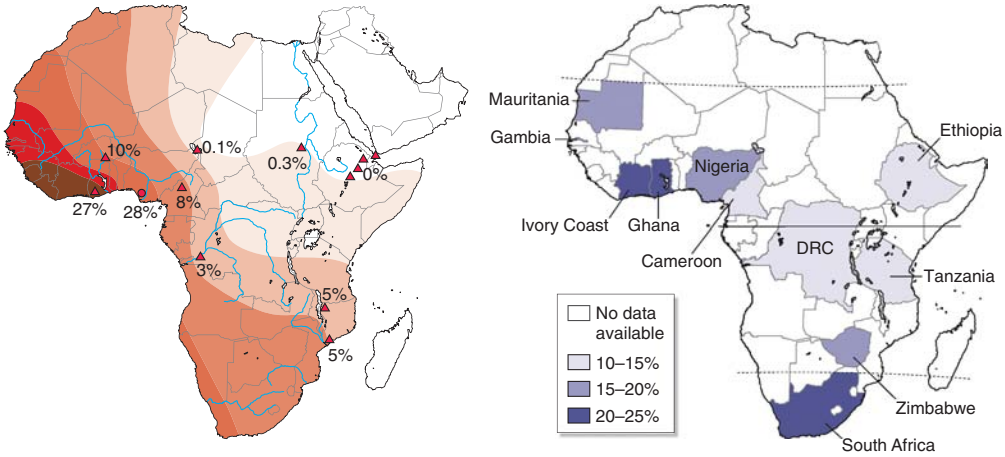

Figure 1 | Maps of distribution of *APOL1* allelic variant frequency and hypertension in certain geographic regions of the African continent. Left: Contour map of allele frequency distributions of identified *APOL1* risk variants in Africa. The combined risk genotype frequency given for Nigeria incorporates data extrapolated for the Yoruba population, and frequencies are likely to differ for other population groups. (Figure adapted with permission from Rosset *et al.*[7]) Right: Geographical representation of hypertension prevalence in continental Africa. (Reproduced with permission from Twagirumukiza *et al.*[14,15])

integrity. Moreover, the genetic epidemiology should be more straightforward in the absence of the variable degree of non-sub-Saharan African admixture seen in other study venues. For example, recently released guidelines of the British Hypertension Society provide very clear directives that categorize African-ancestry subjects together as a homogeneous group in terms of recommendation of calcium blockers as the preferred initial antihypertensive modality (http://www.nice.org.uk/nicemedia/live/13561/56015/56015.pdf). In this regard, it will be important to know whether *APOL1* genotype should be an additional guiding factor in making the antihypertensive choice that is most appropriate for a given person.

So too, at the level of clinical trial design, the genetic epidemiology component that Lipkowitz *et al.* have so importantly added in the aftermath of the AASK trial and cohort study should now become part and parcel of future clinical trials in this and other areas. It is likely that clinical trials that do not incorporate the technical capacity, and meet the regulatory standards for DNA analysis, will fall short of being able to reach meaningful conclusions. In the case of observational epidemiology, this has been amply proven by the recent mendelian randomization that dissociated the causative relationship between high-density lipoprotein levels and coronary disease risk.[14] With appropriately designed, prospective, interventional trials, stratification by categories delineated with the tools of population genetics will likely become the standard approach unifying conventional and genetic epidemiology.

Another interesting feature of the study by Lipkowitz *et al.*[4] is the strong association of *APOL1* G1 risk allelic state with kidney disease that is distinctly not characterized by high-grade proteinuria. This raises the question of the other genetic or environmental factors that determine whether the patient with two parental risk alleles at *APOL1* will develop no disease throughout his or her lifetime, non-proteinuric chronic kidney disease accompanied by hypertension, or one of the high-grade proteinuria glomerulopathies. This question brings us back to the urgent need to understand the biology of *APOL1* risk allele-associated kidney injury. As the authors point out, this may be the only comprehensive and definitive means of developing effective preventive and therapeutic interventions that preserve kidney function, if blood pressure control—as important as it is for prevention of other potentially catastrophic cardiovascular complications—proves simply not to offer kidney protection in the at-risk African-ancestry population.

DISCLOSURE

The authors declared no competing interests.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contribution of Shay Tzur in adapting Figure 1 (left), the contour map of allele frequency distributions of identified APOL1 risk variants in Africa.

REFERENCES

1. Appel LJ, Wright JT Jr., Greene T *et al.* Intensive blood-pressure control in hypertensive chronic kidney disease *N Engl J Med* 2010; **363**: 918–929.
2. Klag MJ, Whelton PK, Randall BL *et al.* Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; **334**: 13–18.
3. Marcantoni C, Ma LJ, Federspiel C *et al.* Hypertensive nephrosclerosis in African Americans versus Caucasians. *Kidney Int* 2002; **62**: 172–180.
4. Lipkowitz MS, Freedman BI, Langefeld CD *et al.* Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 2013; **83**: 114–120.
5. Genovese G, Friedman DJ, Ross MD *et al.* Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**: 841–845.
6. Tzur S, Rosset S, Shemer R *et al.* Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet* 2010; **128**: 345–350.
7. Rosset S, Tzur S, Behar DM *et al.* The population genetics of chronic kidney

disease: insights from the MYH9-APOL1 locus. *Nat Rev Nephrol* 2011; **7**: 313–326.
8. Kanji Z, Powe CE, Wenger JB *et al.* Genetic variation in APOL1 associates with younger age at hemodialysis initiation. *J Am Soc Nephrol* 2011; **22**: 2091–2097.
9. Kopp JB, Nelson GW, Sampath K *et al.* APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011; **22**: 2129–2137.
10. Tzur S, Rosset S, Skorecki K *et al.* APOL1 Allelic Variants are associated with Lower Age of Dialysis Initiation, and thereby Increased Dialysis Vintage in African and Hispanic Americans with Non-diabetic End Stage Kidney Disease. *Nephrol Dial Transplant* 2012; **27**: 1498–1505.
11. US Renal Data System. *2012 USRDS Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health: Bethesda, MD, USA. http://www.usrds.org/2012/pdf/v2_condensed_ref_tables_12.pdf 2012.
12. Reeves-Daniel AM, DePalma JA, Bleyer AJ *et al.* The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant* 2011; **11**: 1025–1030.
13. Tobe SW, Poirier L, Tremblay G *et al.* Challenges and scientific considerations in hypertension management reflected in the 2012 recommendations of the Canadian Hypertension Education Program Open Medicine 2012; **6**: e127–133.
14. Voight BF, Peloso GM, Orho-Melander M *et al.* Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; **380**: 572–580.
15. Twagirumukiza M, De Bacquer D, Kips JG *et al.* Current and projected prevalence of arterial hypertension in sub-Saharan Africa by sex, age and habitat: an estimate from population studies. *J Hypertens* 2011; **29**: 1243–1252.

see clinical investigation on page 104

Dialysis time, survival, and dose-targeting bias

John T. Daugirdas[1]

Dialysis time is increasingly being appreciated as an important measure of dialysis adequacy. Increased dialysis time leads to better control of volume excess, to reduced occurrence of intradialytic hypotension, and to better control of serum phosphorus. Nevertheless, the amount of benefit obtainable by moderate increases in dialysis time in patients following a three-times-per-week schedule has not been well established, and the analysis is confounded by associations between prescribed and/or delivered dialysis time and factors related to patient mortality.

Kidney International (2012) **83,** 9–13. doi:10.1038/ki.2012.365

In this issue of *Kidney International*, analyzing a cohort of prevalent patients being dialyzed mostly three times per week with 3- to 5-hour session lengths, Flythe *et al.*[1] report on the association between prescribed dialysis treatment time and survival. They found a substantial mortality increase associated with slightly shorter prescribed session length.

Controlling for body size is important when analyzing effects of components of dialysis treatment on survival, because body size and dialysis prescription normally are somewhat confounded: one main target of dialysis is to achieve a minimum urea reduction ratio. In small patients a given urea reduction ratio can more easily be achieved with a relatively short dialysis session length; thus, smaller patients and patients with low total body water (such as women) typically will be dialyzed for shorter periods than larger patients and, especially, large men. For reasons not yet clear, smaller hemodialysis patients have a markedly increased mortality. If no adjustment is made for body size, when mortality is found to be increased in patients receiving shorter dialysis treatments, it is not clear whether the effect is due to treatment time alone or was partly or completely mediated by body size. On the other hand, it remains possible that the shorter treatment time usually given to smaller patients is causally related to their increased mortality risk, and in this case, adjusting the outcomes analysis for body size might result in an underestimation of the true risk of shorter treatments.

The usual method of adjusting for body size is to consider some measure of body size, be it weight, anthropometric estimates of total body water or body surface area, volume, or body mass index, as a covariate. Flythe *et al.*[1] used a matching strategy, in which patients of a given size being prescribed a dialysis time less than 4 h were matched with similar-sized patients being prescribed a dialysis session longer than 4 h. Secondary matching by age, sex, and vascular access type also was done. When mortality rates in the less-than-4-hour and more-than-4-hour groups were compared, there was a very substantial difference in mortality, with the group being prescribed less than 4 h (mean delivered time, 201 min) having a 26% higher mortality than the size-matched patients undergoing the longer treatments (mean delivered time, 240 min).

The concept that dialysis time *per se* might be an important measure of dialysis adequacy, beyond urea reduction ratio or urea Kt/V, is an old idea that has been rediscovered and is gaining increasing traction. Because urea is a small, highly diffusible molecule, urea can be rapidly removed from the body by high-efficiency dialysis. This is true especially in smaller patients, women, and children, in whom the volumes of distribution of urea are relatively small. With short, rapid dialysis, however, it is more difficult to remove partially seques-

[1]*Division of Nephrology, Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois, USA*
Correspondence: *John T. Daugirdas, Division of Nephrology, Department of Medicine, University of Illinois College of Medicine, 820 South Wood Street, Chicago, Illinois 60612, USA.*
E-mail: jtdaugir@uic.edu