The *APOL1* Long-Term Kidney Transplantation Outcomes Network—APOLLO

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Clin J Am Soc Nephrol 13: 940–942, 2018. doi: https://doi.org/10.2215/CJN.01510218

Molecular genetics has altered our understanding of the epidemiology and treatment of CKD; >30% of blacks with ESKD have apoL1 gene (*APOL1*)–associated disorders, including FSGS, HIV-associated nephropathy, sickle cell nephropathy, severe lupus nephritis, and solidified glomerulosclerosis with secondary hypertension (1). Presumably caused by natural selection on the basis of protection from African sleeping sickness, *APOL1* nephropathy risk variants are common and present nearly exclusively in populations with recent African ancestry. There is limited understanding of disease mechanisms. This phenomenon contributes to marked racial disparities in CKD in the United States and can result in shorter patient survival and reduced quality of life.

Kidney transplantation remains the preferred treatment for patients with ESKD, including those with *APOL1*-associated nephropathy. Transplantation yields longer survival and better quality of life at lower cost than dialysis. However, a critical shortage of kidneys exists, and deceased donor allograft survival declines over time. Retrospective studies detected more rapid failure of kidneys transplanted from deceased donors with *APOL1* high-risk genotypes (2). This could explain why kidneys donated by blacks, on average, fail more rapidly after transplantation than kidneys from white donors (3). Racial differences in the relative prevalence of blood types and HLAs cause black donor kidneys to more often be transplanted into black recipients than recipients from other racial groups. Between 2008 and 2012, 22% of black deceased donor kidney transplant (DDKT) recipients received kidneys from blacks compared with 11% of white recipients ($P<0.001$; Scientific Registry of Transplant Recipients) (B.I.F., unpublished observations). If donor *APOL1* risk genotypes contribute to more rapid failure of transplanted kidneys, black recipients would be affected more than other race groups. Determining *APOL1* genotypes in kidney donors with recent African ancestry could better predict outcomes after kidney transplantation (4). Rapid *APOL1* genotyping is now available in Clinical Laboratory Improvement Amendments–certified laboratories. Thus, it is possible to determine *APOL1* genotypes in deceased black kidney donors and recipients of their kidneys before transplantation.

The United Network for Organ Sharing (UNOS) creates policies to optimize use of available donor organs by serving as the Organ Procurement and Transplantation Network (OPTN) in the United States transplant system. Before the *APOL1* discovery, the OPTN developed the Kidney Donor Risk Index (KDRI) to improve allocation of deceased donor kidneys by quantitatively estimating the quality of kidneys and linking this information with recipient health (5). The KDRI includes ten deceased donor characteristics, including self-reported race. One intention of the KDRI was to prolong allograft survival by better matching donor kidneys with recipients. Because black donor kidneys, on average, fail more quickly after transplantation than kidneys from donors of other races, the KDRI assumes that all kidneys recovered from blacks have an equal risk for early graft failure. The KDRI was instituted before studies revealed that donor *APOL1* genotypes might contribute to racial disparities in DDKT outcomes (2). Donor *APOL1* genotype effects on allograft survival in DDKT from black donors seem comparable with (or stronger than) established risk factors for allograft failure, such as HLA match, cold ischemia time, and sensitization on the basis of panel reactive antibodies. The KDRI downgrades the quality of all kidneys donated by blacks. However, only 13% of the population possess *APOL1* high-risk genotypes and may be at risk for early graft failure.

No study has prospectively obtained *APOL1* genotype data on donors and recipients to test whether reduced kidney allograft survival is due to donor/recipient *APOL1* genotypes or whether other *APOL1* second gene or environment interactions exist between donors and recipients. Potential benefits and ethical considerations for genotyping prospective black living kidney donors as well as implications for more broadly genotyping the general living donor pool also require clarification (6). Transplantation of a kidney from a healthy living donor with two *APOL1* nephropathy risk variants has been associated with FSGS with early allograft failure in recipients as well as subsequent ESKD in the donor (7). The frequencies with which this occurs are unknown. Although rates of eGFR decline seem similar in high-genetic risk donors and non-donors, 11% of *APOL1* high-genetic risk living donors in the largest study developed ESKD ($P=0.02$), and more developed stage 3 or higher CKD compared with low-genetic risk donors after 12 years ($P<0.01$).

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Although performed at some centers, the practice of genotyping potential living donors for *APOL1* is controversial (8,9). There remains a paucity of data on *APOL1* in living kidney donors, and the UNOS requires follow-up for only 2 years.

Recruitment for the National Institutes of Health–sponsored *APOL1* Long-Term Kidney Transplantation Outcomes Network (APOLLO) will soon begin. The APOLLO provides the opportunity to replace the race term with *APOL1* genotype in the KDRI and assess whether the revised KDRI more accurately reflects donor kidney quality. Results from the APOLLO could improve policies for matching donors with recipients to prolong allograft survival. The long-term health of living kidney donors with high-risk genotypes will also be assessed. The APOLLO will prospectively assess effects of *APOL1* nephropathy risk variants in kidney donors with recent African ancestry and the recipients of their kidneys for outcomes after DDKT and living donor kidney transplantation. Organ procurement organizations and HLA genotyping centers in the United States and Puerto Rico will attempt to collect blood and DNA from all black, Afro-Caribbean, Hispanic black, and African deceased kidney donors for genotyping. Kidney transplant programs will be contacted by one of 13 APOLLO Clinical Centers and asked to work with them by enrolling consenting, eligible living kidney donors and recipients. The APOLLO Coordinating Center at Wake Forest School of Medicine will support studies to determine the effect of donor and recipient *APOL1* genotypes on kidney transplant outcomes in individuals who received a kidney from a donor with recent African ancestry and follow African ancestry living kidney donors for changes in vital status, kidney function, and proteinuria. Initial follow-up of recipients of deceased donor kidneys will be approximately 3–4 years, and longer follow-up is possible with electronic data capture.

The APOLLO includes a 26-member Community Advisory Council that is composed of blacks who have kidney disease, donated a kidney, received a kidney transplant, or have family members with CKD. The Community Advisory Council was involved from the start, providing critical insights into ethical considerations, protocol development, the informed consent process, and conduct of the study. The APOLLO aligned with the UNOS, the Association of Organ Procurement Organizations, the American Society of Transplantation, and the American Society for Histocompatibility and Immunogenetics. An External Expert Panel reviewed the final protocol and will closely monitor study progress with the Community Advisory Council. Results have the potential to inform revision of the national organ allocation policy, prolong allograft survival, and result in reduced rates of organ discard. In addition to effects on the recipients of kidney transplants, the APOLLO may provide data relevant to *APOL1*-associated CKD in native kidneys. Results could also provide critical safety data for potential living kidney donors (10).

The primary APOLLO outcome is time to death-censored kidney allograft failure on the basis of donor and recipient *APOL1* genotypes. Secondary outcomes include effects of *APOL1* on the rate of change in the Chronic Kidney Disease Epidemiology Collaboration equation eGFR computed with the nadir outpatient serum creatinine concentration and follow-up outpatient serum creatinine concentrations at 6-month intervals, rate of change in serum creatinine concentration computed with the nadir outpatient value and follow-up outpatient values at 6-month intervals, and time to development of overt proteinuria. The rate of change in kidney function and quantitative proteinuria from baseline predonation levels will also be assessed in living kidney donors.

At enrollment, a single urine and blood sample will be collected for the APOLLO biorepository from consenting donors and recipients. Thereafter, the bulk of follow-up will be electronic on the basis of data from the UNOS, the US Renal Data Systems, and the National Death Index. This minimizes effort at transplant programs and streamlines data collection. The APOLLO participants will receive usual treatment and follow-up at their transplant center. They will have the option of receiving their *APOL1* genotype data from the study research laboratory several years into the study.

The APOLLO will prospectively perform an analysis of all kidney transplants involving deceased and living donors with recent African ancestry in the United States and Puerto Rico during a specified recruitment period. Prospective data on kidney transplants, donors, and recipients will be collected, and *APOL1* genotyping will be performed. Graft failures and other clinical outcomes will be collected during follow-up. This design is suited to address the APOLLO Consortium's aims of assessing the effect of donor *APOL1* genotype as a predictor of early kidney transplant failure and functional outcomes in recipients and on postdonation kidney function, proteinuria, and vital status in living kidney donors. The APOLLO will assess whether computing the KDRI with *APOL1* genotype instead of the race variable can better predict longer kidney transplantation survival and lessen discard of good-quality kidneys (4). Despite strong retrospective data, implementation of *APOL1* nephropathy risk variant screening in deceased kidney donors requires data from a well powered national prospective study (2,9). The APOLLO is a major step toward a more comprehensive approach to kidney transplantation. The investigators look forward to working with all United States transplant programs on this exciting study.

Acknowledgments

This work was supported by National Institutes of Health grants R01 DK084149 (to B.I.F.), R01 DK070941 (to B.I.F.), and U01 DK116041 (to B.I.F.).

The content of this article does not reflect the views or opinions of the American Society of Nephrology (ASN) or the *Clinical Journal of the American Society of Nephrology* (CJASN). Responsibility for the information and views expressed therein lies entirely with the author(s).

Disclosures

Wake Forest University Health Sciences and B.I.F. have rights to an issued United States patent related to *APOL1* genetic testing (www.apol1genetest.com). B.I.F. is a consultant for Ionis and AstraZeneca Pharmaceuticals.

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Published online ahead of print. Publication date available at www.cjasn.org.