HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2022 April 09.

Published in final edited form as:

Kidney Int. 2021 July ; 100(1): 27–30. doi:10.1016/j.kint.2020.11.025.

APOL1 genotyping in kidney transplantation: to do or not to do, that is the question? (pro)

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Dogma, a principle laid down by authorities as incontrovertibly true, is difficult to change once proven incorrect. Considering chronic kidney disease (CKD) in African Americans, the dogma that nearly 40% have mild-moderate hypertension as the cause of nephropathy, low-level proteinuria excludes glomerular disease, and focal segmental glomerulosclerosis is a nonspecific pathology was suddenly struck down with discovery of association between the apolipoprotein L1 gene (*APOL1*) and nondiabetic CKD.[1,2] *APOL1* G1 and G2 kidney-risk variants (KRVs) display the strongest genetic association in complex disease; G0 is nonrisk. KRVs are found virtually only in populations with recent African ancestry and provide protection from African sleeping sickness.[3] Possessing 2 KRVs, autosomal recessive inheritance (G1G1/G2G2/G1G2, 1 KRV from each parent) defines high-risk genotypes with markedly increased risk for CKD. Approximately 13% of African Americans possess 2 KRVs, and 87% have *APOL1* low-risk genotypes (~39% G0G1/G0G2; ~48% G0G0).[3]

APOL1 subsequently impacted the transplant community. Retrospective data revealed deceased donor genotypes associate with more rapid failure of kidney allografts from African American donors.[4] *APOL1* also contributes to higher risk of end-stage kidney disease (ESKD) in African American live kidney donors.[5] Marked differences exist in health care access, socioeconomic status, and health outcomes between African Americans and European Americans. These disparities are unacceptable and remediable, and society must rapidly address them. One reason transplant surgeons may be reluctant to employ *APOL1* genotyping is the belief that it makes a minor contribution to risk for nephropathy. However, biologic factors account for much of the excess risk for CKD in African Americans.[6]

Although dogma is hard to eradicate, abundant evidence currently supports application of the *APOL1* discovery in transplant medicine. Physicians often order genetic testing to evaluate live kidney donor candidates whose relatives have Mendelian disorders, such as autosomal dominant polycystic kidney disease, inherited podocytopathies, Alport syndrome, and Fabry disease.[7] They exclude potential donors with causative variants. The only difference between these scenarios and *APOL1* is that KRVs are limited to African-derived

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populations and possessing a high-risk genotype translates into an approximate 20% likelihood of CKD.[6] Most individuals with high-risk genotypes do not develop CKD, likely because they lack a second hit. It is unclear what the precise likelihood of developing ESKD after donor nephrectomy is. Because not all individuals with an *APOL1* high-risk genotype develop CKD, some argue this diminishes the value of testing. We feel a 20% risk for CKD is of tremendous clinical importance.

African American kidney donors with *APOL1* high-risk genotypes can develop proteinuric focal segmental glomerulosclerosis and ESKD years after donation; some recipients developed ESKD from focal segmental glomerulosclerosis. A retrospective study in 136 African American donors provides the best available data.[5] As in the general population, 14% had *APOL1* high-risk genotypes. Relative to low-risk donors, *APOL1* high-risk donors had significantly lower mean predonation estimated glomerular filtration rates (98 ± 17 vs. 108 ± 20 ml/min per 1.73 m^2, respectively [$P = 0.03$]). The baseline estimated glomerular filtration rate in both groups was normal; this made it difficult to determine if preexisting kidney disease was present. After median 12-year follow-up, high-risk donors had significantly faster rates of kidney function decline. An estimated glomerular filtration rate <60 ml/min per 1.73 m^2 was seen in 67% of high-risk versus 36% of low-risk donors ($P = 0.01$), and 11% of high-risk donors developed ESKD (vs. 0% of low-risk donors; $P = 0.02$). Results urge caution in performing donor nephrectomies in *APOL1* high-risk live donors. Given the mean age at donation was 37 years, 67% of these donors can be expected to have stage 3 or higher CKD by the age of 49 years, and more will progress to ESKD in middle age. Another report by Locke *et al.* lacked outcome data from live donors.[8] It is the obligation of transplant physicians to protect potential donors from serious outcomes.

We need prospective data in African American live donors based on *APOL1* to determine effects on donor kidney function and health, as well as recipient outcomes. The National Institutes of Health–sponsored "*APOL1* Long-Term Kidney Transplantation Outcomes" (APOLLO) Network is addressing these questions.[9] APOLLO was powered to detect *APOL1* effects in deceased donor transplantation and is collecting DNA from as many African American live donors as possible. An APOLLO Ancillary Study, "Living Donor Extended Time Outcomes," is retrospectively analyzing large numbers of African American kidney donors for *APOL1* genotype, kidney function, and proteinuria with better power. These studies will provide critical information on the safety of live kidney donation and outcomes of transplantation from *APOL1* high-risk donors. APOLLO may inform whether recipients could benefit from learning donor *APOL1* genotypes before proceeding with kidney transplantation.

It is critical to increase the number of kidney transplants from African American live donors. If we provide reassurance to individuals in families having multiple relatives with ESKD that they lack *APOL1* high-risk genotypes, they may be more likely to donate because of lower risk of progression to CKD. APOLLO attempts to reduce barriers for the African American population disproportionately affected by ESKD and more often receiving kidneys from African American donors, some with *APOL1* high-risk genotypes. Although prospective data will take time, existing data strongly support this conclusion. Recall that 87% of African Americans have low-risk genotypes. We reported suggestions for

incorporating *APOL1* genotyping in the live donor workup.[7] As in APOLLO, we suggest discussing the role of *APOL1* in CKD and transplantation with all who report recent African ancestry and offering genotyping to those who remain candidates after initial screening. By excluding candidates with nephropathy or contraindications to donation, the numbers offered genotyping will be lower and fewer high-risk genotypes detected.

Genotyping never should be mandatory; it is the patients' choice. Transplant physicians and donor candidates should have a frank discussion about *APOL1*, and informational materials are available to assist.[9] Until APOLLO is complete and provides national guidance, individual programs need to decide how to counsel those with high-risk genotypes who are otherwise candidates for donation. To protect high-risk individuals, some programs do not recommend proceeding; others consider age cutoffs and input from the donor. Transparency is key. Donor candidates deserve as much information as possible to assist with decision making.[10–12]

There are abundant data on effects of *APOL1* in deceased donor kidney transplantation.[13] Rapid genotyping is available; results can be ready with hepatitis and HIV screens. Retrospective outcomes in 1153 kidney transplants from 624 unique African American donors at 113 programs revealed donor *APOL1* high-risk genotypes were associated with twice the risk of graft failure.[4] A multivariate analysis, including donor age, recipient age, recipient sex, cold ischemia time, panel reactive antibody titer, human leukocyte antigen match, standard versus expanded criteria donor, and center, revealed the hazard ratio for time to renal allograft failure related to donor *APOL1* was 2.05 ($P = 0.0003$).[4] The effect was independent from factors typically considered by transplant teams (cold ischemia time and donor age) and placed *APOL1* at the center of predicting likelihood of kidney allograft survival. Replacing the "race" component in the Kidney Donor Risk Index with *APOL1* genotype would reclassify the Kidney Donor Profile Index in African American donors. The Kidney Donor Profile Index in the ~85% of African American donors with low-risk genotypes would decrease 18 points and increase by 19 points in the ~15% of donors with high-risk genotypes. This net 37-point impact should improve the assessment of deceased donor kidney quality and reduce organ discard.[14] Expected effects include increased numbers of transplants, better matching donors with recipients, and reduced costs.[14] APOLLO is prospectively analyzing these outcomes.

Transplant physicians (and genetic counselors, when needed) should discuss the risks and benefits of *APOL1* testing in understandable terms before ordering genotyping (Table 1). They should also be available to address concerns after results return. APOLLO developed participant infographics for these purposes, describing implications of high-risk versus low-risk genotypes.[9] Potential kidney donors must understand that ~80% of individuals with *APOL1* high-risk genotypes will not develop CKD and individuals with low-risk genotypes could still develop non–*APOL1*-associated kidney disease. Before testing, patients should be informed about the Genetic Information Nondiscrimination Act, intended to protect from discrimination in the workplace or when purchasing health insurance. If an individual opts for testing, he/she does not have to inform others or provide results. Indications for *APOL1* genotyping exist outside of kidney transplantation (family planning and risk of nephropathy in patients with HIV and lupus).[15,16] If a safe and effective treatment for *APOL1*-associated

nephropathy becomes available, the frequency of testing would be expected to increase. Novel treatments for *APOL1*-associated nephropathy are undergoing testing and could prove useful in transplantation. Nonetheless, genetic testing has risks, and results can be stressful to some. That is why genotyping is a personal choice and should never be undertaken lightly. Testing may prevent inadvertent harm to donors who provide an altruistic service that benefits recipients.

It is time to end the dogma that African American donor race is the risk factor for shorter kidney allograft survival; the donor *APOL1* genotype conveys risk. Transplant physicians should discuss *APOL1* genotyping with all African American live donor candidates. This relatively inexpensive test should make kidney donation safer and will likely increase the number of donors. *APOL1* genotyping in African American deceased donors should improve the kidney allocation process, reduce discards, and increase the number of good quality kidneys for transplantation.

ACKNOWLEDGEMENTS

Sincere thanks to Ana Iltis, PhD; Alejandra Mena Gutierrez, MD; and Amber Reeves-Daniel, DO, for their helpful review of the manuscript. Support provided by the National Institutes of Health R01 DK070941, R01 DK084149, R01 MD009055, and U01 DK116041 (to BIF) and U01 DK116097 (to EDP).

DISCLOSURE

Wake Forest University Health Sciences and BIF have rights to an issued US patent related to *APOL1* genetic testing. BIF is a consultant for, and receives research funding from, AstraZeneca and RenalytixAI. The other author declared no competing interests.

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Table 1 |

Considerations for *APOL1* genotyping in African ancestry live donor candidates

Consideration	Comments
Discuss *APOL1* effects in CKD and transplantation	Provide sufficient time before donor nephrectomy
If candidate after initial workup, offer genotyping	Do not mandate genotyping
What are the potential donor's wishes?	May not want to proceed if high-risk genotype
What is the transplant program's protocol?	Local guidance for *APOL1* high-risk candidates
Discuss potential benefits of genotyping	Potential to make live donation safer Personal right to know
Discuss potential risks of genotyping	Genetic Information Nondiscrimination Act Results could cause stress
Provide information before and after testing	Clinician expert (or genetic counselor) Individual may (or may not) want to disclose testing was performed or inform others of their result

CKD, chronic kidney disease.