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Cases in Precision Medicine: *APOL1* and Genetic Testing in the Evaluation of Chronic Kidney Disease and Potential Transplant

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This article discusses potential indications for genetic testing in an African American patient with chronic kidney disease who is being evaluated for a kidney transplant. Two known risk variants in the *APOL1* (apolipoprotein L1) gene predispose to kidney disease and are found almost exclusively in persons of African ancestry. *APOL1* risk variants are considered, including whether clinicians should incorporate genetic testing in the screening process for living kidney donors. In addition to *APOL1* testing, the role of diagnostic exome sequencing in evaluating potential transplant recipients and donors with a positive family history of kidney disease is discussed.

We present a hypothetical case to illustrate the potential role of genetic testing in the setting of kidney disease and a kidney transplant evaluation.

A 35-year-old African American man returned to our office with his wife to discuss the results of his recent kidney biopsy, which showed focal segmental glomerulosclerosis (FSGS). He now has chronic kidney disease (CKD), stage 3. He has a brother who is receiving dialysis for hypertension-associated end-stage renal disease (ESRD) and is concerned that he too will need dialysis. He has read about the genetic risk for kidney disease due to the *APOL1* (apolipoprotein L1) gene and asks whether genetic testing should be performed.

What Do We Know About *APOL1*'s Role in CKD?

Two common coding sequence variants in *APOL1*—G1 and G2—strongly predispose persons of African ancestry to kidney disease (1). These variants confer disease risk in an

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autosomal recessive manner so that persons with the 0 or 1 variant do not have increased risk, whereas those with 2 variants (G1/G1, G1/G2, or G2/G2 genotype) are at markedly higher risk for kidney disease, including FSGS (odds ratio, 17 [95% CI, 11 to 26]), HIV-associated nephropathy (odds ratio, 29 [CI, 13 to 68]), and hypertension-associated ESRD (odds ratio, 7.3 [CI, 5.6 to 9.5]) (1, 2). The observation that kidney allografts transplanted from *APOL1* high-risk genotype donors to low-risk recipients fail sooner than kidneys from *APOL1* low-risk donors (3–5) suggests that increased kidney disease risk is probably the result of variant protein being expressed in the kidney itself.

The *APOL1* risk variants are found predominantly in persons of sub-Saharan African ancestry and account for a substantial portion of the increased kidney disease risk in African Americans (1). Similar to the way in which sickle cell trait protects against malaria, the heterozygous *APOL1* genotype protects against African trypanosomiasis (sleeping sickness) (6). Although the risk genotype is almost nonexistent in European and Asian populations, it appears in up to 15% of African Americans and may be found in Hispanic and other populations whose admixed genetic makeup might include a large African component (7–9). Thus, the question of genetic testing arises in anyone with substantial African ancestry (10).

Most persons with the *APOL1* risk genotype do not develop CKD; in one study with up to 21 years of follow-up, CKD developed in only 33 of 404 participants with the *APOL1* risk genotype (11.6 events per 1000 person-years), and ESRD developed in only 25 of the 404 (3.4 events per 1000 person-years) (11). The low penetrance is probably the result of a more complex genetic model, in which exposure to additional genetic or environmental risk factors—or “second hits”—is required to uncover the effect of the *APOL1* risk genotype. However, other second hits remain unknown, hindering potential preventive management of persons at risk.

Is Testing for *APOL1* Gene Variants Useful in a Patient With FSGS or CKD?

The AASK (African American Study of Kidney Disease and Hypertension) examined 693 African Americans with CKD attributed to hypertension. The primary outcome, a composite of ESRD or a doubling of serum creatinine level, occurred in 58.1% of patients in the *APOL1* high-risk group versus 36.6% of those in the *APOL1* low-risk group (hazard ratio, 1.88 [CI, 1.46 to 2.41]) (12). The CRIC (Chronic Renal Insufficiency Cohort) study examined 2955 patients of European and African descent with CKD (46% with diabetes). Similar to observations in AASK, *APOL1* high-risk genotype was associated with a more rapid decline in estimated glomerular filtration rate (eGFR) and a higher risk for renal disease progression. Of note, among the patients with diabetes, the eGFR slope (expressed in milliliters per minute per 1.73 m^2 per year) was −1.5 among European Americans, −2.7 among African Americans in the *APOL1* low-risk group, and −4.3 among African Americans in the *APOL1* high-risk group. Among the patients without diabetes, the corresponding eGFR slopes were −0.7, −1.0, and −2.9 mL/min/1.73 m^2 per year. The faster rate of renal function loss in the *APOL1* high-risk group remained significant after adjustments for demographic, socioeconomic, and clinical risk factors in both diabetic and nondiabetic groups (12). Furthermore, in patients with FSGS, *APOL1* high-risk genotype has been associated with an earlier age of onset and faster progression to ESRD (hazard

ratio, 2.3 [CI, 1.43 to 4]) (2). Together, these data demonstrate that *APOL1* risk genotypes are associated with accelerated kidney disease progression, regardless of the specific cause of the kidney disease.

On the basis of these data, knowledge of *APOL1* genotype in a patient with CKD of any cause would seem helpful. However, the precise mechanism of *APOL1*-mediated kidney damage remains unknown, and knowledge of *APOL1* risk status in patients with the disease does not change treatment recommendations at present. Studies have shown that in patients with FSGS, *APOL1* genotype is not associated with differences in treatment response to steroids (2), cyclosporine, or mycophenolate mofetil–dexamethasone (13). Therefore, *APOL1* testing in an African American patient with a new diagnosis of FSGS or CKD generally is not recommended at this time, primarily because the result would not be clinically actionable and would not rule out the possibility of other Mendelian or acquired forms of disease.

Our patient continues to come for regular follow-up appointments. During the next few years, his renal function deteriorates, until finally we discuss the possibility of a kidney transplant. Several of his relatives offer to be evaluated as potential donors.

What Is the Role of *APOL1* Gene Testing in the Setting of Kidney Donor and Recipient Evaluation?

The donor's *APOL1* status, and not the recipient's, seems to have an effect on long-term allograft survival, at least on the basis of the currently available retrospective data (3–5, 14). Although recipients of kidneys from deceased donors with 2 risk variants have a 27% graft failure rate at 5 years (4), mortality among patients receiving hemodialysis is now almost 60% at 5 years (15). Therefore, the key question regarding *APOL1* genetic testing centers around the living donor's well-being. Of importance, transplantation is an operation for which the donor derives no medical benefit; thus, proper assessment and discussion of the long-term risks of kidney donation are essential.

Strict screening criteria for living kidney donors are applied to prevent a potential donor from being placed at high risk for kidney disease later in life. Although all potential living donors undergo a rigorous evaluation, evidence shows that kidney donors are at increased risk for hypertension (16) and proteinuria (17), and a small subset of persons, particularly African Americans, do develop ESRD after donation (18, 19). Although case reports of ESRD in donors with 2 *APOL1* risk variants already exist, a small retrospective cohort study recently demonstrated that donors with 2 risk variants had a lower GFR at the time of donation, more rapid decline in GFR, and increased risk for ESRD, raising concern regarding the uncertainty of the magnitude of risk associated with nephrectomy (20–22).

The primary concern is whether nephrectomy might serve as a second hit, unmasking detrimental effects of an *APOL1* risk genotype, and thus accelerate a decline in renal function or worsen the prognosis of a donor who is exposed to other second hits later in life. Often, patients' family members are considered as possible kidney donors, and they themselves are more likely to carry *APOL1* variants and—if they do—to develop kidney

disease (Table and Supplement, available at Annals.org). They also may share with the intended recipient similar risks for exposure to an environmental second hit. The issue of *APOL1* screening therefore is especially relevant in evaluating potential living, related kidney donors.

Other demographic and clinical factors are associated with a person's risk for ESRD and should be incorporated into discussions with potential donors regarding *APOL1* testing and their risk for ESRD, despite the associated complexities. For example, although older age is associated with a higher 15-year incidence of ESRD, younger age is associated with a higher lifetime projected incidence of ESRD (23). This is probably because older persons who have not yet developed ESRD are less likely to do so, whereas young people have decades ahead in which ESRD may develop. Age and other factors may interact with the increased risk conveyed by the *APOL1* high-risk genotype and thus must be discussed with patients in connection with *APOL1* testing and risk for ESRD.

African Americans are at higher risk than persons of other ancestries for ESRD after kidney donation. In a study of 96 217 living donors in the United States who donated kidneys between 1994 and 2011, the cumulative incidence of ESRD at 15 years was more than 3-fold higher for African Americans than for European Americans (74.7 vs. 22.7 events per 10 000) (19, 21). Because the risk variants are present exclusively in people of African ancestry, this association may be partially explained by *APOL1*. However, confirming the detrimental role of nephrectomy in donors with *APOL1* risk variants is a challenge. The effects of donation in this population are unlikely to manifest for years, so long-term follow-up of donors to observe these effects is needed. Furthermore, the consequences of high-risk genotype on donation may depend on additional genetic or environmental exposures, which necessitates a cohort with comprehensive data on a wide variety of exposures.

A large prospective multicenter study called APOLLO (*APOL1* Long-Term Kidney Transplantation Outcomes) began recently and is prospectively recruiting both deceased and living African American kidney transplant donors and their recipients across the United States. The study's findings will be used to assess the effects of *APOL1* genotype on long-term outcomes for both recipients and living donors (24). In the meantime, we lack conclusive answers regarding the risks of kidney donation in someone with the *APOL1* risk genotype.

Because of the paucity of evidence-based knowledge regarding the risks of kidney donation by persons with the *APOL1* risk genotype, formal recommendations regarding what to do with genotype information do not exist. Thus, we turn to concepts in medical ethics to inform our recommendations for donor screening.

The Belmont Report (25), a foundational text of medical ethics, describes 3 principles that may be applied to donor *APOL1* testing. The first is respect for persons. Recently, this principle has been understood in terms of relational autonomy, which includes both the patient's right to make decisions and the health care team's duty to help the patient make decisions that best reflect his or her interests and values. Through shared decision making, patients and physicians discuss the available information and together arrive at a decision

that is best for the patient. In our case, this process would involve providing the potential donor with information about *APOL1*, discussing the donor's priorities, and reaching a conclusion about whether to perform the test and what to do with the results. Community deliberations with African American patients have shown that many support the option of testing, especially in a transplant context (26), and physicians should be ready to engage in these discussions. In shared decision making, the physician must ensure that the patient has a clear understanding of the options and their risks and benefits; this may be particularly difficult in cases like ours, in which the risks of having the *APOL1* genotype remain ambiguous in the setting of kidney donation.

The Belmont Report's second principle is beneficence. This concept includes nonmaleficence, also referred to as *primum non nocere*—first do no harm—and is put into practice by weighing the risks and benefits in a given situation. Debate continues in the transplant field regarding whether we have enough information at this time to make informed recommendations regarding donor *APOL1* testing (27, 28). Because we remain uncertain as to how to use knowledge of the *APOL1* genotype most effectively, genotype testing may lead to anxiety without providing clear benefits. In addition, the potential donor may value the risks and benefits to the allograft recipient and weigh those as well in his or her considerations.

The third principle is justice, which includes fair and equal treatment, and nonexploitation of vulnerable persons or groups. In our situation, this rule might require us to ensure that no person feels undue pressure to make a particular medical decision, whether it be to have *APOL1* testing or not or to donate a kidney or not. It also requires a guarantee that no group will bear an undue burden of the consequences of testing. *APOL1* is specific to African ancestry, and African American patients already face large disparities in living organ donation. *APOL1* testing of only African American donors may potentially reduce the pool of available donors and thus may have a substantial negative effect on African American recipients (27, 29, 30).

In summary, several essential clinical and ethical considerations regarding donor testing must be addressed, but no clear-cut answers exist. Of most importance, more evidence is clearly needed to better understand postdonation risks in persons carrying the *APOL1* high-risk genotype. Because of the current ambiguity, we recommend shared decision making with patients who are at increased risk for having the *APOL1* risk genotype, including African American donors and donors with relatives known to have the *APOL1* risk genotype. At this time, the data seem insufficient to inform unilateral policies. Although some transplant centers have instituted *APOL1* criteria to include or exclude potential donors, we recommend caution regarding this practice until more evidence on donation risks becomes available. Instead, physicians should offer possible *APOL1* testing along with referral to a genetic counselor, discuss possible steps after testing and the risks and benefits to the donor and recipient, and help the patient incorporate his or her values into the decision of how to proceed if the test result is positive.

If the Kidney Transplant Donor and Recipient Are Interested in *APOL1* Testing After Discussion of What Is Known About the Risks and Benefits in the Setting of *APOL1* Risk Genotype, Who Should Be Tested?

If a potential donor opts for *APOL1* testing, we recommend referring the person to a genetic counselor and then testing him or her directly, without involving the potential transplant recipient. By excluding the recipient from these discussions, we avoid the possibility of the recipient pressuring the potential donor to undergo testing he or she does not want or persuading the donor to reveal the *APOL1* test results, which otherwise would remain protected health information. In this way, potential donors can make their own medical decisions and maintain confidentiality regarding these decisions and results.

In the Setting of a Family History of Kidney Disease, Are Genetic Tests Other Than *APOL1* Testing Indicated?

Because our patient has a positive family history of ESRD, an alternative genetic cause of kidney disease must be considered. The most commonly known genetic causes of adult-onset FSGS include pathogenic variants in *COL4A3–5* (collagen, type IV, α−3) (10% to 38%), *INF2* (inverted formin 2) (3.6% to 17%), *TRPC6* (transient receptor potential cation channel, subfamily C, member 6) (2.5% to 20%), *ACTN4* (actinin, α−4) (1.25% to 3.5%), and *PAX2* (paired box gene 2) (4%) (31). Also, new causes of monogenic FSGS are being discovered each year, and they may be present independent of *APOL1* genotype; thus, they should always be considered when FSGS is diagnosed in a patient with a positive family history, independent of *APOL1* testing results (32). Similar to *APOL1*, other genetic causes of FSGS may place relatives at increased risk after kidney donation.

Exome sequencing (ES) is a technique that sequences most of the protein-encoding portions of the genome. It may be particularly efficient for the molecular diagnosis of kidney diseases, such as FSGS, because of a large degree of genetic heterogeneity. Recent studies indicate that in patients with all-cause CKD, ES can help detect variants relevant to the diagnosis of underlying disease as well as to nephrology care (33, 34). The diagnostic yield of ES is as high as 17% for adult patients with CKD of unknown cause, although its precise diagnostic yield in the setting of adult-onset FSGS awaits large-scale investigation (34). Of note, the yield seems even greater in pediatric patients with ESRD of unknown cause (35).

Given the positive family history in this case, we would consider either ES or gene panel testing to search for other genetic causes of adult-onset FSGS, which also may be present in related potential donors. We would recommend a conversation with the patient and his relatives about the potential benefits of ES, similar to the discussion regarding *APOL1* testing. In contrast to *APOL1* testing, however, we would recommend ES for the prospective recipient first. If a pathogenic variant is detected, potential related donors may then be tested by targeted sequencing to assess their donation eligibility.

Summary of Recommendations and Limitations

On the basis of small retrospective studies, the *APOL1* risk genotype of kidney donors—not of recipients—seems to be associated with decreased kidney allograft survival. We recommend against systematic *APOL1* testing in prospective recipients at this time, because the results are not clinically actionable. More robust data are needed to determine whether living donors with the *APOL1* high-risk genotype are at increased risk for kidney disease after donation (Key Summary Points). In the meantime, we recommend discussing the risks and benefits of *APOL1* testing with potential kidney donors during evaluation, and referring the prospective donor to a genetic counselor if he or she decides to have genetic testing. In addition, for potential recipients with a positive family history of kidney disease, ES should be considered to search for other pathogenic variants that may underlie familial disease. Future research on the utility of ES in evaluating living, related kidney donors is still needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Summary Points

At this time, *APOL1* (apolipoprotein L1) genetic testing in persons of African ancestry with a new diagnosis of focal segmental glomerulosclerosis or chronic kidney disease generally is not recommended, even in the presence of a positive family history.

APOL1 risk genotype may represent a risk factor for renal disease after kidney donation, but rigorous studies assessing the magnitude of potential risks have not yet been performed.

The clinical utility of genetic testing for *APOL1* in evaluating potential living donors of African ancestry remains unclear.

Discussing *APOL1* testing with prospective donors directly, without involving the recipients, protects the donor's privacy by avoiding situations in which the recipient might pressure the potential donor to undergo testing or to share the results.

Recent data suggest that diagnostic exome sequencing should be considered in evaluating familial kidney disease in the setting of kidney transplant assessment, especially for a prospective recipient with familial disease whose blood relatives are being considered as potential donors.

Table 1.

Approximate Probability That a First-Degree Relative of an African American Kidney Recipient Has the *APOL1* Risk Genotype, Given Knowledge of the Recipient's Genotype*

Recipient's *APOL1* Genotype	Probability That a Relative Has *APOL1* Risk Genotype			
	Parent	Sibling	Child	Spouse (or Unrelated)
Risk genotype	0.39	0.48	0.39	0.15
Nonrisk heterozygous	0.19	0.13	0.19	0.15
Nonrisk homozygous	0	0.04	0	0.15
Unknown	0.15	0.15	0.15	0.15

APOL1 = apolipoprotein L1 gene.

* Conditional probabilities were calculated on the basis of autosomal recessive inheritance and a baseline risk genotype frequency of 15% for U.S. African Americans (Supplement, available at Annals.org). The calculations are only approximate, because they assume a single risk allele and all family members self-identifying as African American. Nonetheless, these estimates clearly illustrate large differences in pretest probabilities when the recipient's genotype is already known.