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African American Living-Kidney Donors Should Be Screened for *APOL1* Risk Alleles

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Abstract

The adjusted rate of end-stage kidney disease (ESKD) among African Americans is markedly increased relative to European Americans. African Americans are overrepresented on the kidney transplantation waiting list and experience longer wait times. In aggregate, these pressures drive recommendations for living donor transplantation. Genovese et al. recently implicated the *APOL1* gene in ESKD risk among African Americans (Genovese et al. *Science* 2010; 329: 841). The presence of two *APOL1* risk alleles doubles the relative risk for ESKD; moreover, the alleles are prevalent among African Americans. We propose a strategy for screening for the presence of *APOL1* risk alleles among African American living kidney donors and for living-related donors for African American recipients.

Keywords

Genetics; Allele; Kidney

The increased incidence of chronic and end-stage kidney disease (ESKD) among African Americans has important implications for kidney transplant recipients and donors alike. In the most recent data available, the adjusted rate of incident ESKD was more than three times as high in African Americans as European Americans, and the rate of hypertensive ESKD among African Americans in the 30- to 39-year-old age group was more than 10 times as high as their European American counterparts (1). African Americans comprise a disproportionately high fraction of the kidney transplantation waiting list and experience longer wait times (2). Therefore, there are unique pressures converging to promote live

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kidney donation among African Americans. At the same time, accruing evidence indicates an increased risk of eventual ESKD in African American kidney donors relative to other racial groups (3, 4). Particularly alarming is the small but recognized subset of donors experiencing rapid (i.e., <5 years) progression to ESKD; in one report, African Americans comprised 9 of 10 donors in this category (3). Therefore, strategies to minimize the risk of ESKD among African American donors—while preserving donor availability—are urgently needed.

A substantial percentage of ESKD among African Americans is either poorly characterized or attributed without biopsy to hypertensive ESKD. The basis for increased susceptibility to hypertensive ESKD among African Americans has generated a great deal of interest and speculation. Data from the MrFIT trial showed that even after taking into account the impact of blood pressure, the incidence of ESKD was more than double (and up to five times as high) in African Americans relative to European Americans (5). This blood pressure-independent effect has been ascribed to a variety of environmental factors disproportionately affecting African Americans; however, in a detailed analysis, sociodemographic factors, lifestyle factors, and clinical variables accounted for less than half of this increased ESKD risk (6). Although there may be environmental factors not captured by this analysis, it is reasonable to speculate that a genetic basis may contribute to an observed difference in disease frequency between racially or ethnically distinct populations.

When the incidence of a clinical condition differs between genetically “overlapping” populations, admixture mapping can be used to determine which regions of the genome contribute to the observed difference in phenotype (7). Admixture of formerly isolated populations gives rise to a genetic “shuffling” over successive generations; this shuffling is a consequence of both chromosomal segregation and smaller chromosomal crossover events occurring during meiosis. Over many generations, the descendants’ genomes become mosaics of the original populations’ genomes. For example, in the United States, African American chromosomes typically reflect 11% to 15% European ancestry (8). When the genomes of disease-affected patients are compared with controls, the genomic regions in which the disease-prone ancestry is overrepresented among affected patients are inferred to contribute to the disease association.

Admixture mapping was used to identify a locus on chromosome 22 that is associated with nondiabetic ESKD and focal segmental glomerulosclerosis (FSGS) in African Americans (9, 10). Of the many genes in the vicinity, *MYH9* generated the most enthusiasm because amino acid-changing point mutations in the gene were previously associated with a hereditary form of glomerulonephritis (11). Subsequent investigations in African American ESKD patients, however, failed to uncover specific *MYH9* variants likely to impact function or expression level of the gene product (e.g., Ref. 12).

Genovese et al. (13) took a fresh approach. Armed with data emerging from the 1000 Genomes Project (www.1000genomes.org), they searched a broader interval around *MYH9* for genetic variants that were common in African individuals and that also showed large differences in allele frequency between Africans and Europeans. They next tested these genetic variants for association with biopsyproven FSGS in African Americans. They

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identified two gene variants strongly associated with FSGS; both resided not within *MHY9* but within the adjacent *APOL1* gene. In support of a possible functional role, one variant coded for two closely spaced amino acid substitutions in the ApoL1 protein (the “G1” allele), and the second coded for a deletion of two adjacent amino acids in the same vicinity (the “G2” allele). The strong association was confirmed in a group of over a thousand African Americans diagnosed with hypertensive ESKD, when compared with geographically matched African American controls. Importantly, the variants were common, representing 62% to 75% of *APOL1* alleles in those affected with kidney disease, and 33% to 34% of alleles in unaffecteds. A single copy of a “risk” allele (G1 or G2) conferred only a modest increase in ESKD odds (OR=1.26); however, two copies of a risk allele had a dramatic effect, increasing the odds ratio to greater than seven (OR=7.3, relative to zero risk alleles), consistent with a recessive genetic model (13). When recalculated as a relative risk rather than odds ratio, the risk of developing ESKD was more than doubled by the presence of two risk alleles (relative to zero risk alleles), and two risk alleles were present in 46% and 12% of the ESKD and non-ESKD subjects, respectively.

The most remarkable aspect of this set of observations, however, arose from evidence supporting selection for these apparent risk-associated alleles; they were of relatively recent origin and had rapidly achieved high prevalence in some African populations. The ApoL1 protein is the lytic factor in blood tasked with killing circulating trypanosomal parasites. Genovese et al. went on to show that incorporation of the risk allele-associated amino acid substitution(s) gave rise to an ApoL1 protein that was far more efficient at killing a deadly endemic subspecies of the *Trypanosoma* parasite responsible for “sleeping sickness” (African trypanosomiasis). Furthermore, this effect was a dominant one—only a single copy of a variant *APOL1* allele was required to enhance killing. These stunning data closely paralleled the well-described heterozygote advantage model in sickle cell disease: one copy of the variant allele confers protection from a lethal infectious disease, whereas two copies are profoundly deleterious.

It is expected that genotyping for the presence of *APOL1* variants will supplant that of *MYH9* as ESKD risk alleles. Enthusiasm for the latter had been tempered by a lack of mechanistic insight; in addition, the *APOL1* variants are more strongly associated with kidney disease (13). Utility of *MYH9* genotyping in the kidney transplant population had received only limited mention (14, 15). Interestingly, although it is now clear why *APOL1* ESKD-associated risk alleles underwent evolutionary selection, and although the mechanism through which these alleles impact trypanolytic activity has been convincingly shown, the mechanistic connection to kidney disease remains obscure. Until this relationship is clarified, it is conceivable that additional genetic variants in tight linkage disequilibrium with the *APOL1* risk alleles (i.e., coinherited with them) may confer the kidney phenotype.

One can argue how (or whether) these data should be used to inform care of African American patients with hypertensive or nondiabetic CKD; thus far, there are no specific therapies tailored to *APOL1* variant-associated CKD or ESKD, and there are no data addressing efficacy of “standard” ESKD prophylactic measures (e.g., rigorous blood pressure control or pharmacological inhibition of the renin-angiotensin-aldosterone axis) in this population. However, the implications that emerge in the transplantation population are

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striking. First-degree relatives are often sought as potential living donors, and close relatives of African American ESKD patients are likely to share one or more *APOL1* risk alleles. The biological child of an African American patient with *APOL1*-associated ESKD will almost undoubtedly have inherited a risk allele from that parent (because most affected patients will be homozygous for a risk allele, i.e., G1/G1 or G2/G2, or compound heterozygous, G1/G2); moreover, because the frequency of the risk alleles is substantial in the general African American population, there is a reasonable chance of inheriting a second risk allele from the other parent. Therefore, first-degree relatives of African American patients with hypertensive or nondiabetic ESKD (or idiopathic or HIV-associated FSGS) are likely to have an increased risk of developing ESKD, even in the absence of kidney donation.

It has been proposed that race is a “social construct” and not inherently biologically based; however, the completion of the Human Genome Project and application of data generated by the International HapMap Consortium and the 1000 Genomes Project make clear that percentage of African and European (and any other) genetic ancestry can be estimated with reasonable precision at the population and individual levels. Whether one self-identifies as African American, the presence of two *APOL1*-associated risk alleles may predispose to ESKD. Also, although virtually all African American genomes reflect some European-Middle Eastern ancestry, self-identification as African American was an excellent proxy for African ancestry (8). Specifically, among African American populations across four separate regions of the United States, an average of 69% to 74% ancestry was traceable to the predominant West, Central, and South African ancestral (Niger-Kordofanian) population (8). We infer that self-identified African American race is a reasonably robust—albeit fraught and imperfect—index of genetic ancestry.

At our institutions, we are embarking on a program to screen potential living-related donors for self-identified African American recipients, as well as self-identified African American potential donors for any recipient. The presence of a single *APOL1* risk allele will not impact donor eligibility; however, the presence of two risk alleles will constitute a relative contraindication to donation. We infer from the data of Genovese et al. (13) that the relative risk of developing ESKD with two disease-associated alleles is more than doubled, relative to that with zero risk alleles. We anticipate that this effort will protect potential donors with two risk alleles from an injudicious reduction in nephron number.

Until more extensive data are available, we do not propose that two *APOL1* disease-associated alleles constitute an absolute contraindication to donation. Such a policy would introduce the risk of further restricting the donor pool for African Americans awaiting kidney transplantation. Based on data from the control groups in Genovese et al., one could infer that approximately one in eight potential donors not destined for renal disease could be excluded from the donor pool based solely on *APOL1* genotype; however, it should not be concluded from these data that members of the control group with two risk alleles would never have developed CKD or ESKD simply because they appeared to be unaffected when the study was conducted. In addition, prohibiting donation with two risk alleles may unduly constrain a potential donor’s informed decision-making capacity in the unique and emotionally charged setting of parent-to-child kidney transplantation. Potential donors with two risk alleles will require meticulous consenting with attention to what is known—and

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what is still unknown—about their propensity for ESKD. Candidates declining donation on the basis of their genotype will be recommended for close follow-up with attention to blood pressure, clearance, and proteinuria. Data supporting a prophylaxis and/or treatment regimen tailored to those with two copies of an *APOL1* risk allele would be welcome.

An additional caveat concerns the indirect impact of genotyping. Knowledge of an increased risk of ESKD may lead to emotional stress. In addition, loss of privacy—as with all health information—may adversely affect insurability or employability. However, eligibility decisions under the current system (i.e., in the absence of *APOL1* genotyping) are routinely predicated on the likelihood of a potential donor developing advanced CKD or ESKD postnephrectomy; therefore, informing a potential donor of an increased ESKD risk based on genotype differs little, conceptually, from providing the same prognostic information in the context of previously unrecognized proteinuria, for example. Either entails an emotional burden. Furthermore, recent evidence indicated an absence of psychological stress among individuals who had chosen to undergo genotyping for a broad panel of known or suspected disease-associated risk alleles (16).

From a practical standpoint, genotyping for *APOL1* risk alleles will be relatively inexpensive. Genomic DNA is routinely obtained for human leukocyte antigen typing. We project a cost of less than $200 per sample for polymerase chain reaction-based amplification and direct (“Sanger”) sequencing of the affected *APOL1* exon; however, batch processing and higher throughput genotyping approaches should permit dramatic economies of scale. In contrast to introducing a new biochemical test, where assay sensitivity, reagent variability, and differing local thresholds for an abnormal call can lead to “center effects,” genotyping is robust and reproducible. The most vexing issues are likely to be (1) sample integrity (ensuring correct assignment of the genomic DNA to the patient) and (2) DNA amplification integrity (ensuring that the patient’s DNA—rather than a contaminating amplicon—is being genotyped). Both of these issues are readily addressed by restricting the *APOL1* genotyping to Clinical Laboratory Improvement Amendments-certified laboratories enrolled in polymerase chain reaction and/or genotyping quality control programs.

As an aside, although our program does not propose testing donors who have already undergone nephrectomy, this population may (retrospectively) afford a unique window into the pathogenesis of *APOL1*-associated ESKD. Specifically, the half-life of transplanted kidneys from African American donors with two *APOL1* risk alleles could be compared across various recipient groups (e.g., recipients with zero vs. two risk alleles) to assess the relative contributions of kidney-specific and kidney-extrinsic factors in initiating and promoting *APOL1*-associated renal disease. While the present manuscript was undergoing initial review, Reeves-Daniel et al. (17) elegantly addressed one element of this question. Their report considered only the fate of the allograft and not that of the donor, whereas the present focus has been on outcome of the living donor. Allograft survival was assessed among 136 recipients of kidney transplants from African American deceased donors, as a function of allograft—and not recipient—*APOL1* genotype. After a mean follow-up of slightly more than 2 years, the incidence of graft loss was more than doubled when the allograft donor carried two *APOL1* risk alleles (relative to zero or one risk allele). Other potentially confounding donor and recipient characteristics (e.g., recipient race and donor

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terminal creatinine) were unlikely to have accounted for this difference (17). These data suggest either (1) the allograft harboring two *APOL1* risk alleles was already subclinically and perhaps irreversibly damaged at the time of harvest or (2) the allograft with two risk alleles is genetically programmed for premature failure after transplantation.

The role of donor *APOL1* genotype in recipient-centered outcomes is beginning to generate interest (17). We predict that the role of this genotype in live donor outcomes will be equally important, if not more so. In summary, we believe that knowledge of the genetics of ESKD risk among African Americans has matured to the point that ascertainment of *APOL1* risk allele status among potential live kidney donors should be used to inform clinical decision making in assessing donor suitability and/or eligibility.

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