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Editorial

APOL1 Genotyping of African American Deceased Organ Donors: Not Just Yet

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Variants of the apolipoprotein L1 (*APOL1*) gene have been linked to a variety of renal diseases in individuals of African ancestry including focal segmental glomerulosclerosis and hypertension-attributed nephropathy (1). Two common coding variants in the *APOL1*gene (G1 and G2), known to impart resistance to *Trypanosoma* infections, appear to confer most of the renal-associated risk. Patients with two copies of the coding variants are at highest risk while those with one allele have similar risk to patients with zero alleles (2). The *APOL1* risk alleles are common in individuals of African ancestry occurring in more than 30% of chromosomes but are very rare in those of European descent (<1%) (1). In both the African American Study of Kidney Disease and Hypertension and in the Chronic Renal Insufficiency Cohort study, African American patients with two variants had approximately a 1.5 to 2-fold increased risk for end-stage renal disease or doubling of creatinine and more rapid rate of CKD progression compared to those with zero or one allele (2).

These nontransplant studies on *APOL1* provide a compelling rationale to examine whether the *APOL1* risk effects explain partly or fully, the well-established inferior allograft survival seen in African American recipients or in those who receive African American donor kidneys. In a small study involving 119 African American kidney transplant recipients, Lee et al found no difference in graft survival in high-risk *APOL1* (two alleles) compared to low-risk (zero or one allele) recipients (HR 0.96; 95% CI 0.61–1.49; p = 0.84) (3). In a single center study from North Carolina, Reeves-Daniel et al examined outcomes from 106 African American deceased donors, of whom 22 (21%) had two *APOL1* copies, and found that two *APOL1* variants in a deceased donor was independently associated with a greater risk of graft failure (HR 3.84; p = 0.0.84) (4). In this issue of *AJT*, Freedman et al follow-up on this original report from North Carolina by including new deceased donors from their state as well as from Alabama (5). In this analysis, they report outcomes on 675 kidney transplants performed at 55 centers (two centers accounted for 62% of transplants) from 368 African American deceased donors. The transplants spanned many years with some being done as early as 2001 while approximately 25% were performed after 2010. Of the 675 transplants, 99 (15%) were from donors with two *APOL1* risk variants and during follow-up 24 of these 99 (24%) failed. In an adjusted model involving the entire cohort, recipients who received a donor kidney with two *APOL1* alleles had over a twofold increased risk of graft failure (HR 2.26; 95% CI 1.37–3.74; p = 0.001). Despite a larger sample (n = 221), two *APOL1* alleles was not independently associated with graft loss in recipients of Alabama donor kidneys (HR 2.71; 95% CI 0.95–7.69) while it was in the original cohort of 127 patients from North Carolina (HR 2.33; 95% CI 1.10–4.90). Examination of the survival curves reveals that most grafts failed within the first 2 years posttransplantation, although *APOL1* risk variants were not associated with delayed graft function or acute rejection.

What should we make of this data? The authors suggest we genotype deceased donors for *APOL1* and use this information to guide allocation and informed consent. This recommendation is premature and is not supported by the research findings in the manuscript by Freedman et al or other published work. It is also potentially injurious to African American transplant candidates who may receive fewer transplants if such donor kidneys are excluded. We believe that the article by Freedman et al raises more questions than it answered. The limitations diminish the weight of evidence to warrant recommending using *APOL1* risk status to inform deceased donor organ allocation. First, it remains unknown why these allografts failed. Could these graft losses be due to unrecognized antibody injury or some other insult such as BK virus infection? In this regard, allograft biopsy data would be critically informative. Perhaps recipients of donors with two *APOL1* variants just need heightened surveillance to prevent or quickly treat a ''second hit'' such as an infection or rejection. Second, when the analysis was further adjusted by including time on dialysis, recipient diabetes status and BMI the HR for graft

loss fell from 2.26 to 1.99 suggesting confounding and the possibility of residual confounding cannot be excluded. Thirdly, recipient *APOL1* genotyping was not available and despite the previously mentioned negative findings (3) an interaction between donor and recipient risk variants cannot be excluded. Fourth, the study showed an *association* with *APOL1* risk variants which is not the same as causality. It is possible that other genes may be directly involved in the cascade of events leading to graft failure. Finally, the number of graft losses in the entire *APOL1* high risk group was only 24 and follow-up beyond 2 years occurred in a very small number of patients.

The retrospective analysis by Freedman et al has not produced evidence to support the use of *APOL1* genotyping in deceased donor transplantation because of the inherent limitations of the study noted above. The next step forward should be a geographically broader, multi-center, prospective cohort study to obtain highly granular phenotype data to answer the unresolved questions. To be methodologically rigorous, the optimal study would include all consecutive donors at several distinct OPOs and the analysis should take into account information on immunosuppression, preimplantation biopsies, posttransplant complications (e.g. infections), donor specific antibody using modern solid phase assays, and biopsies for cause to determine the precise phenotype of the grafts that fail with two *APOL1* risk variants. Only with such a rigorous study can we precisely define the true impact of *APOL1* renal risk variants on allograft survival. Premature use of this data to guide kidney allocation is decidedly unwarranted and is likely to disadvantage African American patients waiting for a transplant, result in more discards, and contribute to lower wait list survival for those who should have been transplanted.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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