The *APOL1* Gene and Allograft Survival after Kidney Transplantation

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Coding variants in the *apolipoprotein L1* gene (*APOL1*)
are strongly associated with nephropathy in African
Americans (AAs). The effect of transplanting kidneys
from AA donors with two *APOL1* nephropathy risk
variants is unknown. *APOL1* risk variants were geno-
typed in 106 AA deceased organ donors and graft
survival assessed in 136 resultant kidney transplants.
Cox-proportional hazard models tested for association
between time to graft failure and donor *APOL1* geno-
types. The mean follow-up was 26.4 ± 21.8 months.
Twenty-two of 136 transplanted kidneys (16%) were
from donors with two *APOL1* nephropathy risk vari-
ants. Twenty-five grafts failed; eight (32%) had two
APOL1 risk variants. A multivariate model account-
ing for donor *APOL1* genotype, overall African ances-
try, expanded criteria donation, recipient age and gen-
der, HLA mismatch, CIT and PRA revealed that graft
survival was significantly shorter in donor kidneys
with two *APOL1* risk variants (hazard ratio [HR] 3.84;
p = 0.008) and higher HLA mismatch (HR 1.52; p =
0.03), but not for overall African ancestry excluding
APOL1. Kidneys from AA deceased donors harboring
two *APOL1* risk variants failed more rapidly after renal
transplantation than those with zero or one risk vari-
ants. If replicated, *APOL1* genotyping could improve
the donor selection process and maximize long-term
renal allograft survival.

Introduction

Two coding variants in the *apolipoprotein L1* gene
(*APOL1*) are strongly associated with nondiabetic forms of
nephropathy in African Americans (AAs) in an autosomal
recessive pattern of inheritance (1, 2). *APOL1* nephropathy
risk variants include G1, a nonsynonymous coding variant
(342G:384M), and G2, a six base pair deletion. The *APOL1*
gene variants are strongly associated with hypertension-
attributed end-stage renal disease (HA-ESRD, typically fo-
cal global glomerulosclerosis [FGGS] with interstitial scar-
ring and arteriolar changes), idiopathic focal segmental
glomerulosclerosis (FSGS) and HIV-associated collapsing
glomerulosclerosis in AAs, with odds ratios of 7.3 and
10.5 (recessive), respectively, for HA-ESRD and FSGS (1–
3). *APOL1* risk variants likely rose to high frequency in
sub-Saharan Africa due to the protection they afford from
Trypanosoma brucei rhodesiense infection, the parasite
causing African sleeping sickness (1).

Variation in *APOL1* accounts for the higher rate of nondi-
abetic kidney disease in AAs relative to European Amer-
icans (1). Thirty percent of AA chromosomes possess
either a G1 or a G2 *APOL1* allele (alleles are mutually ex-
clusive on single chromosomes); approximately 10–12%
of AAs possess two *APOL1* risk variants and 49% lack risk

variants (1). In comparison, *APOL1* risk variants are rare in European Americans, approximately 0.3% carry G1 and 0.1% G2 alleles (4).

Kidneys donated by AAs are known to function for shorter periods of time than kidneys donated by European Americans (5–8). This effect is observed whether kidneys are transplanted into AA or non-AA recipients. We hypothesized that this difference in renal allograft survival rates according to donor race could be secondary to the presence of *APOL1* risk variants. Therefore, we tested for differences in renal allograft survival in kidneys donated by AAs with two *APOL1* nephropathy risk variants versus those with zero or one *APOL1* risk variants.

Methods

Study design
From March 24, 1998 through September 12, 2009, 234 AA deceased organ donors had kidneys recovered and typing material procured or delivered to the Wake Forest University Baptist Medical Center (WFUBMC) for transplantation purposes. DNA from whole blood was available in 106 individuals whose kidneys were subsequently transplanted at the same medical center into 136 unique transplant recipients. These locally performed kidney transplant patients were followed longitudinally at our center for at least 1 year and form the study sample. This study was approved by the WFUBMC Institutional Review Board.

Transplant immunosuppression
Prior to 2001, transplant recipients were managed with cyclosporine, mycophenolate mofetil (MMF) and prednisone immunosuppression with selective use of nondepleting antibody induction (basiliximab or daclizumab). From October 2001 to February 2005 patients received T cell depleting antibody induction with rabbit antithymocyte globulin (rATG) in combination with tacrolimus, MMF and prednisone. From February 2005 to September 2007 patients received rATG or alemtuzumab in combination with tacrolimus, MMF and early steroid elimination. Patients with delayed graft function (DGF) underwent a surveillance kidney biopsy at 2 weeks posttransplant. Tacrolimus target levels and decisions whether to withdraw steroids (after 2005) depended on immunologic risk stratification and initial kidney graft function. Patients considered at higher immunologic risk (retransplants, panel reactive antibody [PRA] levels >20%, AAs <40 years of age) or those with DGF remained on steroids but were tapered to 5 mg/day by 2 months after transplant. High immunologic risk patients were managed with target tacrolimus levels 10–12 ng/mL for the first 3 months, then 8–10 ng/mL. Low immunologic risk patients were tapered off steroids by postoperative day 6, target tacrolimus levels were 8–10 ng/mL for the first 3 months, then 6–8 ng/mL.

Patient follow-up
All transplant recipients were followed closely in the WFUBMC transplant clinic for at least 3 months with a minimum of twice weekly monitoring for the first 6 weeks and then weekly monitoring for the next 6 weeks. Stable patients were referred to their community nephrologist and seen back in the WFUBMC transplant clinic at 6- to 12-month intervals thereafter. Routine laboratory testing at the WFUBMC transplant clinic is performed in the North Carolina Baptist Hospital Central Laboratory. HLA typing, crossmatching and PRA testing were performed in the Wake Forest University Health Sciences HLA/Immunogenetics Laboratory. All evaluations in this report were based on results from these laboratories.

Tissue processing and genotyping
DNA extraction from whole blood was performed using either QIAamp DNA Blood Mini Kits (Qiagen; Venlo, Netherlands) or an AutoPure LS automated DNA extraction robot (Gentra Systems; Valencia, California). Three *APOL1* single nucleotide polymorphisms (SNPs) were genotyped on the Sequenom Mass Array *(www.sequenom.com)*; rs73885319 and rs60910145 in G1 (SNPs in perfect linkage disequilibrium; $r^2 = 1.0$) and rs71785313 in G2. Ancestry estimates were provided by genotyping seventy biallelic ancestry informative markers, as previously reported (9).

Statistical analyses
The distribution of demographic variables for AA kidney donors by *APOL1* risk status was compared using Wilcoxon two-sample tests for continuous variables and chi-square tests for binary variables. A series of Cox-proportional hazard models were then fitted. The 106 deceased donor kidneys transplanted into 136 recipients resulted in correlated but unordered outcomes for 30 kidneys donated by one individual and transplanted into two recipients. We assumed no significant time difference within these 30 clusters, since the transplants were performed within hours of each other and the duration of graft function was measured in years.

The outcome of interest was time to graft failure computed as the difference between the transplant date and the graft loss date (date of return to dialysis). The date of final observation was censored in the event of death or at the final clinical follow-up with a functioning graft. Several marginal (10) Cox-proportional hazard models were fitted starting with an unadjusted model testing for association between the presence of two copies of *APOL1* G1 or G2 nephropathy risk variants (G1 homozygotes, G2 homozygotes or G1/G2 compound heterozygotes) as defined in Genovese et al. (1) and time to graft loss; ending with a fully adjusted model that tested for the same effect after accounting for the proportion of African ancestry in kidney donors, recipient age and gender, HLA match, cold ischemia time, PRA (0% vs. > 0%) and standard (*vs.* expanded) criteria donation. Expanded criteria donors were defined as age 60 years or older; or meeting two of three criteria if age 50–59: history of hypertension, death from stroke or terminal serum creatinine concentration greater than 1.5 mg/dL. The marginal model is akin to the well known generalized estimating equations (11), where unbiased parameter estimates are obtained using pseudo-likelihoods and the sandwich estimate of the covariance is used to account for the within cluster correlation. The marginal model works well for unordered outcomes but may yield biased estimates for ordered outcomes. For completeness, we compared the results of the marginal model to frailty models assuming a Gamma distribution, which yielded the best fit for the data. Both models yielded the same inference in each case (results not shown). Diagnostic tests based on the Schoenfeld residuals showed the proportional odds assumption holds. The minimum p value associated with the interaction effect between all covariates in the final model and log (time to graft loss) was 0.08.

Results

Donor and recipient characteristics in the 136 AA deceased donor kidney transplants are shown in Table 1, contrasting donors having two (N = 22) *versus* less than two (N = 114) *APOL1* nephropathy risk alleles. Although kidneys from donors with two *APOL1* risk alleles were more often transplanted into male recipients (77.3 vs. 53.5%, p = 0.04), other characteristics were similar between the donor groups. Four kidney transplants were performed before 2001 (1 from a donor kidney with two *APOL1* risk variants), 26 between 2001 and 2005 (3 from donors with

Table 1: Demographic characteristics of renal allograft donors and recipients

Variables	Number of APOL1 G1-G2 nephropathy risk variants from kidney donor		
	Two N = 22	Zero or 1 N = 114	p Value
Donor age (years)	43.7 ± 16.8	47.7 ± 15.8	0.27
Donor gender (% male)	66.3	60.0	0.26
Terminal serum creatinine (mg/dL)	1.34 ± 0.8	1.19 ± 0.7	0.51
PRA* at transplant (%)	13.4 ± 27.6	19.7 ± 31.3	0.48
PRA* > 0 (%)	31.6	38.7	0.56
Donor African ancestry (%)	0.77 ± 0.10	0.72 ± 0.21	0.53
Cold ischemia time (hours)	22.5 ± 7.9	23.2 ± 8.0	0.82
HLA mismatch (N)	4.2 ± 1.4	3.8 ± 1.5	0.29
Recipient gender (% male)	77.3	53.5	0.04
Recipient age (years)	45.2 ± 16.9	47.1 ± 16.2	0.72
Standard criteria donor (%)	81.8	79.8	0.83
Recipient race (% African American)	50.0	50.9	0.94
Diabetic ESRD in recipients (%)	27.3	39.5	0.28

*PRA = panel reactive antibody percentage.

Table 2: Fully adjusted model for renal allograft survival

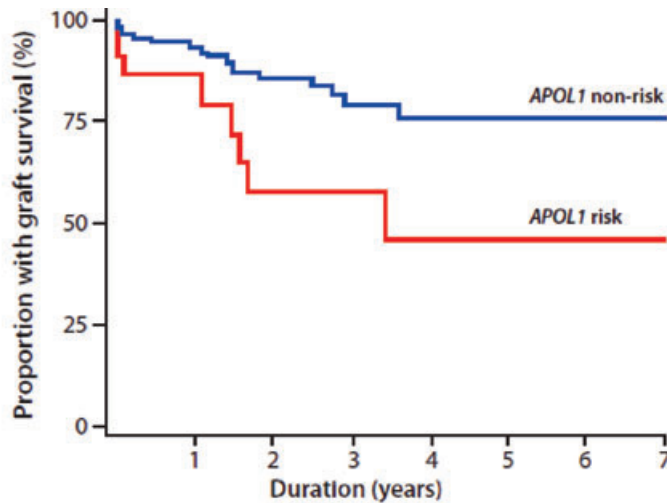| Parameter	Parameter estimate	Standard error	p Value	Hazard ratio
APOL1 G1/G2 (2 vs. 0/1 copies)	1.35	0.51	0.008	3.84
African ancestry	–0.76	1.66	0.65	0.47
Recipient age	0.01	0.02	0.40	1.02
Gender (female)	–0.01	0.52	0.98	0.99
Donor criteria (standard)+	–0.38	0.56	0.50	0.69
HLA mismatch	0.42	0.19	0.030	1.52
Cold ischemia time	0.06	0.03	0.057	1.06
PRA* > 0%	0.33	0.56	0.56	1.39

+Standard versus expanded criteria donor.
*PRA , panel reactive antibody.

of a kidney with none or one APOL1 risk variants. No transplant recipient had a doubling of serum creatinine concentration without ultimate graft loss during the study.

In a model adjusting for genome-wide African ancestry, significantly shorter graft survivals were observed in recipients of donor kidneys with two APOL1 risk variants (hazard ratio [HR] 2.95, p = 0.01). In the fully adjusted model, the presence of two APOL1 risk alleles in donor kidneys independently predicted graft failure (HR 3.84, p = 0.008), after accounting for global donor African ancestry, recipient age and gender, cold ischemia time, PRA, number of HLA mismatches and expanded criteria donation (Table 2). Excluding APOL1, donor African ancestry was not independently associated with graft survival. Higher numbers of HLA mismatches (HR 1.52, p = 0.030) also predicted shorter graft survival, with a trend toward an effect from increased cold ischemia time (HR 1.06, p = 0.057). Figure 1 depicts the Kaplan–Meier curves illustrating renal allograft survival based on the APOL1 genotypes of kidney donors. Recipients of kidneys from donors with one APOL1 nephropathy risk variant had similar renal allograft survivals as those who received kidneys with zero risk variants (p = 0.65).

All cases with graft failure had a kidney biopsy. In the eight cases losing graft function after receiving kidneys from donors with two APOL1 risk variants, potential APOL1-associated lesions were present in 75% (one FSGS, two FSGS collapsing variant and three donor-acquired nephron scarring with arteriosclerosis). These six biopsies were performed after a mean of 74.7 (range 7–183) days, none immediately pre- or postimplantation. The two remaining recipients of APOL1 risk kidneys that failed underwent early nephrectomy (hyperacute rejection day 5; vascular compromise/multiple infarcts day 2). In the 17 cases losing graft function after receiving kidneys from donors with less than two APOL1 risk variants, FSGS was seen in 11.8% (one case each of FSGS and FSGS collapsing variant). Of the remainder, nine had chronic changes associated with rejection, two vascular

two APOL1 risk variants) and 106 after 2005 (18 from donors with two APOL1 risk variants). Donor age, terminal serum creatinine concentration, percentage of recipients who were AA, and percentage of recipients with diabetes-associated ESRD did not differ significantly between recipients of kidneys from donors with two APOL1 nephropathy risk variants versus zero or one risk variants (Table 1). A urinalysis at organ procurement was available in 82 of the 106 deceased donors (14 APOL1 risk donors and 68 nonrisk donors). Trace or greater proteinuria was detected in 5 of 14 APOL1 risk donors (36%) and 22 of 68 (32%) nonrisk donors.

Renal allograft recipients were followed from 0.03 to 127.2 months after transplantation; all patients with less than 1 year of follow-up had graft failure prior to 1 year. The mean follow-up was 27.5 ± 22.2 months in the 126 recipients followed beyond January 1st, 2009. The mean duration of follow-up for the 10 recipients lost to follow-up prior to this date was 12.5 ± 10.3 months and two (20%) of them received kidneys with two APOL1 risk variants. Ten deaths were recorded, one (4.5%) in a recipient of a kidney with two APOL1 risk variants and nine (7.9%) in recipients with either none or one APOL1 risk variant. Twenty-five renal allograft failures were recorded, eight in the 22 recipients (36.4%) of a kidney with two APOL1 risk variants, and 17 (14.9%) in the 114 recipients

APOL1 non-risk

No. at risk	114	82	52	35	18	7	6	3
No. with graft loss (%)	–	7 (6%)	13(11%)	16 (14%)	17 (15%)	17 (15%)	17 (15%)	17 (15%)
No. censored	–	25	49	63	79	90	91	94

APOL1 risk

No. at risk	22	12	8	5	2	1	1	0
No. with graft loss (%)	–	3 (14%)	7 (32%)	7 (32%)	8 (36%)	8 (36%)	8 (36%)	8 (36%)
No. censored	–	7	7	10	12	13	13	14

compromise/multiple infarcts, two donor-acquired diabetic glomerulosclerosis (both on postimplantation biopsy), one thrombotic microangiopathy and one hyperacute rejection. Excluding 5 of 17 with postimplantation biopsies, the other 12 biopsies were performed after a mean of 446 (range 8–1248) days.

Multivariate analysis was repeated excluding graft failures due to hyperacute rejection and technical failure, processes felt unlikely to be *APOL1* related. Excluding 2/8 graft losses from *APOL1* risk donors and 3/17 graft losses from *APOL1* nonrisk donors, two *APOL1* G1/G2 risk variants in donors (HR 2.32, p = 0.028) and number of HLA mismatches (HR 1.68, p = 0.025) remained significantly associated with graft survival, with weaker effect from cold ischemia time (HR 1.06, p = 0.10).

Discussion

In this single center study, significantly shorter renal allograft survival was observed in patients receiving deceased donor kidneys from AAs with two *APOL1* nephropathy risk variants compared to patients receiving kidneys from AA donors with fewer than two risk variants. Differences in graft survival were seen after approximately 20 months. Accounting for risk variation in *APOL1*, overall African ancestry did not significantly impact renal allograft survival after transplantation. HLA mismatch also significantly contributed to graft survival; however, the hazard ratio was

weaker than that for *APOL1* risk variants. In addition, we have shown that long-term renal graft survival rates in AA deceased donors lacking two *APOL1* risk variants are similar to the rates seen in both non-AA deceased donor recipients listed in the US Renal Data Systems between 1994–1998 (6) and in standard criteria deceased donor recipients listed between 1997–2007 in the US Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients (22). Therefore, our preliminary findings in a small sample suggest that the shorter renal allograft survival rates seen in kidneys donated by AAs relative to Caucasians could be substantially related to variation in *APOL1*.

The mechanism(s) whereby *APOL1* gene polymorphisms or ApoL1 risk variant proteins contribute to the development of glomerulosclerosis in native kidneys is unknown. The Kaplan–Meier renal allograft survival curves based on *APOL1* genotypes of AA deceased kidney donors separate substantially by 20 months after renal transplantation in this report. Since 75% of failed grafts from donors with two *APOL1* risk variants had FSGS or severe donor-acquired microvascular disease on biopsies shortly after transplantation, this suggests that the presence of two *APOL1* risk variants with the stress of cold ischemia and exposure to calcineurin inhibitors led to accelerated loss of kidney function. We postulate that subclinical nephropathy was likely present in some kidneys donated by *APOL1* risk homozygotes prior to procurement; especially since patients with FGGS often lack significant proteinuria (2). Nephrotoxicity relating to the presence of abnormal circulating

ApoL1 proteins in transplant recipients is unlikely. ApoL1 is synthesized in the liver and would not be impacted by the genotype of the donor kidney. This does not preclude a role for nephrotoxicity initiated by circulating ApoL1 proteins (either free or HDL bound) in the kidneys of risk donors prior to donation. The initiating mechanisms for nephropathy could also differ in patients based upon their histologic subtype of *APOL1*-associated disease (e.g. FSGS, collapsing FSGS as in HIV associated nephropathy and FGGS). This remains an important area of research.

Messenger RNA encoding *APOL1* is expressed in liver, lung, placenta, endothelial cells, weakly in heart and pancreas, and possibly macrophages (12). ApoL1 is a secretory protein that associates with plasma high-density lipoprotein (HDL) cholesterol (13). We hypothesize three potential pathways whereby *APOL1* variants may lead to nephropathy in native (nontransplanted) kidneys. First, ApoL1 variant proteins may circulate in individuals harboring two *APOL1* risk alleles; these proteins may bind less well to HDL particles, remain free to be filtered and reabsorbed by the proximal nephron and cause kidney disease. Circulating ApoL1 proteins have been implicated in rapidly recurring FSGS after kidney transplantation; a syndrome that can be improved with plasmapheresis (14–17). Second, altered HDL concentrations may contribute to the development of renal microvascular disease, a common accompaniment of FSGS and HA-ESRD. This effect may be accelerated in the presence of calcineurin inhibition. Finally, messenger RNA encoding ApoL1 protein is expressed in cultured human podocytes and other renal cell types (unpublished observation; Barry Freedman and Jeffrey Kopp). As such, podocyte expression could lead to injury or failure to support a critical cellular function. ApoL1 shares structural and functional similarities with the Bcl2 family of proteins involved in apoptosis (18). Apoptosis in podocytes may lead to glomerulosclerosis. These pathways, singly or in concert, could contribute to the development of subclinical *APOL1*-associated kidney disease in native kidneys, with subsequent loss of graft function after donation in the presence of cold ischemia and nephrotoxic medications including calcineurin inhibitors.

Additional risk factors for post-kidney transplant allograft failure include deceased donor category, preservation and recipient issues, and exposure to BK polyomavirus infection. These factors could accelerate graft loss in donor kidneys harboring two *APOL1* risk variants. Importantly, significant differences in terminal serum creatinine concentration, donor age, percentage of AA recipients, type of immunosuppression (based on year of transplantation) and percentage of recipients with diabetic ESRD were not observed between study groups. Differential antigen presentation and immune system cell–cell interactions in *APOL1* risk carriers may exist. Known immune–modulatory effects of apolipoprotein E (ApoE), another lipoprotein constituent of HDL, include inhibition of antigen-stimulated T cell proliferation, downregulation of intracellular signaling molecules downstream of the interleukin 2 receptor, suppression of proinflammatory cytokine formation by macrophages, regulation of major histocompatibility complex class II and costimulatory molecules (CD80, CD86) expression on dendritic cells and inhibited expression of adhesion molecules on endothelial cells (19, 20).

Weaknesses of this report include the small sample size, lack of *APOL1* genotype determinations in recipients, few postimplantation biopsies, and results limited to a single transplant center. Recipient *APOL1* genotypes would have permitted analysis of donor–recipient genotype interactions on graft survival (21); an effect relevant only for AA recipients as *APOL1* nephropathy risk variants are rare in Caucasians. In this study, AAs received 50.0% of donor kidneys harboring two *APOL1* risk variants and 50.9% of kidneys harboring zero or one risk variants (p = 0.94), nonetheless recipient genotypes remain of interest. Finally, although this was a single center study, all AA deceased donor kidneys with DNA for *APOL1* genotyping transplanted at our center during the study period were included. This analysis clearly requires replication in other centers, as well as in recipients of live donor renal transplants. We did not adjust for the presence of donor specific antibodies, body mass index, rejection, compliance to medical therapy and follow-up. While we do not believe that differences in these factors contributed to our results, these are additional limitations.

At present, we do not suggest changes in kidney donor selection based on *APOL1* genotypes, as our finding needs to be replicated at other transplant centers. However, our findings suggest that donor kidney *APOL1* genotypes have the potential to improve the donor selection process, potentially resulting in optimization of long-term renal allograft function. If replicated, studies delineating the molecular basis of this finding and the testing of novel strategies to prevent early failure of African-ancestry donor kidneys related to *APOL1* nephropathy risk variants are warranted, in this era of global shortages of suitable kidneys for transplantation.

Acknowledgments

Disclosure

The authors of this manuscript have nothing to disclose as described by the *American Journal of Transplantation*.

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