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Title: Genetic Determinants of Kidney Transplantation Outcomes

Research Question

This project will investigate the contributions of genetic ancestry and African admixture to kidney transplant outcomes of allograft rejection and survival.

Background and Scientific Rationale

Patients with end-stage renal disease (ESRD) who receive a kidney transplant have improved survival[1] and quality of life[2] compared with patients on the waitlist who are receiving hemodialysis. As with all allografts, transplanted kidneys can be rejected at any point, although most allograft rejections occur within the first year post transplantation. Of those who received a kidney transplant in 2011, the probability of all-cause graft failure in the first year was 8% for deceased donor organ recipients and 3% from living donor organ recipients.[3] Improvements in immunosuppressive treatments, interventional and surgical techniques, and management of infection have decreased the rates of short-term rejection of kidney allografts.[4] Research efforts continue to search for factors associated with graft survival in order to improve clinical outcomes further.

Genetic information already has contributed to increased rates of graft survival through better understanding and utilization of HLA matching.[5] In the past few years, genetic polymorphisms have begun to be explored as potential predictors of transplant outcomes, but most candidate gene studies published to date are poorly designed and underpowered. There is speculation that, similar to the way HLA research led to changes in clinical practice and outcomes, the investigation of genetic factors involved in renal transplants could also lead to clinical improvements. Large racial discrepancies in the incidence and prevalence of ESRD, and the etiologies of ESRD, may provide insight into underlying genetic predispositions to allograft loss. In 2008, the incidence of ESRD among African-Americans was 3.6 times that among whites,[6] and African-Americans have higher rates of focal segmental glomerulosclerosis, HIV-associated nephropathy, and hypertension associated chronic kidney disease (CKD) than do other populations.[7] Recent studies have discovered two coding sequence variants (rs73885319 and rs60910145) in the apolipoprotein L1 (*APOL1*) gene, located on Chromosome 22, that account for a significant portion of the increased risk of these types of kidney disease in the African-American population.[8,9] Ongoing research suggests that these variants result in increased endocytic activity and decreased organelle acidification, which may lead to podocyte loss and ultimately kidney disease.[10,11,12] The *APOL1* risk variants have the potential to be used to design more effective strategies for renal transplant allocation. In one study, kidney allografts from deceased African-Americans with two *APOL1* risk variants failed sooner than kidneys from donors with fewer variants; this finding sparked a discussion of whether to replace race with *APOL1* genotype in the algorithm for the Kidney Donor Risk Index.[13]

In this study, we will test the effects of recipient and donor genetic ancestry – their ancestral composition as defined by their genetic variations – and fraction of African admixture on kidney transplant rejection and overall graft survival. We will also determine whether recipient and donor *APOL1* genetic variants affect allograft outcomes. Finally, we will perform discovery

GWAS to search for genetic variants associated with renal transplantation outcomes. Our study will utilize a unique cohort of Columbia renal transplant patients that contains genomic information from over 1200 donor-recipient pairs to date.

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