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The impact of *APOL1*, *CAV1*, and *ABCB1* gene variants on outcomes in kidney transplantation: donor and recipient effects

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Abstract

Dramatic improvements have been seen in short term kidney allograft survival over recent decades with introduction of more potent immunosuppressant medications and regimens. Unfortunately improvements in long term graft survival have lagged behind. The genomics revolution is providing new insights regarding the potential impact of kidney donor genotypes on long term graft survival. Variation in the donor apolipoprotein L1 (*APOL1*), caveolin 1 (*CAV1*), and multi-drug resistance 1 encoding P-glycoprotein genes (*ABCB1*) are all associated with graft survival after kidney transplantation. Although the precise mechanisms whereby these donor gene variants confer risk for graft loss have yet to be determined, these findings provide novel opportunities for modifying interactive environmental factors and optimizing kidney allocation with the ultimate goal of improving long term graft survival rates.

Keywords

ABCB1; *APOL1*; *CAV1*; genetics; kidney disease; transplantation

Introduction

End-stage kidney disease (ESKD) remains a major public health concern with increasing numbers of prevalent patients on dialysis and recent annual Medicare costs exceeding \$29 billion. Kidney transplantation is preferable to dialysis for children and adults with ESKD, leading to improved quality of life and longer patient survival at far lower cost. In 2006 the total Medicare expenditure per person per year approximated \$25,000 for an individual who had received a kidney transplant compared to \$75,000 for dialysis.(2) Although 92% of transplanted kidneys function beyond one year, long term graft loss has remained high despite recent medical advances.(3) As such, new tools are urgently needed to improve long term graft survival, particularly in pediatric and young adult patients to ensure normal growth and prolonged physical function.

The risk of chronic kidney disease (CKD) is jointly influenced by genetic and environmental effects. It is intuitive that nephropathy susceptibility gene variants in kidney donors and

immune response genes in transplant recipients would have the potential to impact long term allograft function. Several recent reports have explored the impact of genetic variants in donor kidneys on allograft survival; including risk variants associated with nephropathy susceptibility, altered drug metabolism, and risk of viral entry into cells. Donor kidneys used for transplantation are an ideal model for evaluating the clinical importance of kidney donor genetic predisposition on long term allograft survival. The combination of reduced nephron mass (transplantation of one kidney) coupled with the environmental stresses of cold ischemia (particularly for deceased donor kidney transplants [DDKT]) and exposure to nephrotoxic medications (calcineurin inhibitors, CNIs) make kidney transplant genetics clinically relevant. The transplant procedure is similar to partial nephrectomy in rodents with subsequent exposure to nephrotoxins; however, kidney transplantation yields information pertinent to human disease.

This manuscript reviews kidney donor genetic variants impacting long term transplant outcomes, including in the apolipoprotein L1 gene (*APOL1*) which appear to explain the effects of African donor ethnicity on graft survival, the caveolin 1 gene (*CAV1*) potentially linked to renal fibrosis and/or ascending BK polyoma virus infection, and multi-drug resistance 1 encoding P-glycoprotein gene (*ABCB1*) impacting drug metabolism. It is highly likely that donor genetic information will be utilized in clinical renal transplantation, providing additional risk stratification beyond traditional risk factors (Table 1). In addition, risk variants in *APOL1* and potentially other genes may one day inform potential living kidney donors of their risk for nephropathy after donation.(4) It is likely that genetic variation beyond the major histocompatibility locus will soon play an important role in transplant medicine and determination of optimal immunosuppression regimens. In pediatric nephrology, the long term success of the first kidney transplant is of the utmost importance; subsequent transplants are more likely to have an inferior outcome due to patient sensitization, increased risks of infection and rejection, and the cumulative burden of immunosuppression.

Apolipoprotein L1 gene (*APOL1*)

The incidence of ESKD in African Americans is 3.4 times higher than in European Americans.(1) *APOL1* risk variant allele frequencies fully explain the excess rate of non-diabetic ESKD between African and European ancestry populations, as well as familial clustering of multiple etiologies of ESKD in single African American families.(5–7) The two nephropathy-associated coding *APOL1* risk variants (G1 and G2) are virtually absent in European and Asian populations with frequencies well below 1%.(8, 9) In contrast, the G1 and G2 risk alleles are very common in African Americans due to positive selection resulting from the survival advantage provided by ApoL1 protein from *Trypanosoma brucei rhodesiense* –induced African sleeping sickness.(5)

Fifty percent of African Americans possess at least 1 *APOL1* risk allele; approximately 12% possess 2 risk alleles and are at substantially increased risk for non-diabetic nephropathy.(5) Possession of 2 *APOL1* risk alleles confers a 29 fold increased risk for HIV-associated nephropathy (HIVAN), 17 fold increased risk for focal segmental glomerulosclerosis (FSGS) and 7.3 fold increased risk for hypertension-attributed ESKD (now known to be in

the spectrum of FSGS and not caused by hypertension).(5, 10, 11) The frequencies of *APOL1* G1 and G2 risk variants appear to be higher among west Africans than African Americans (12) and strikingly lower frequencies of risk variants are found in Ethiopians (east Africa), likely explaining lower rates of HIVAN in Ethiopians despite presence of HIV.(13) *APOL1* risk variants are known to associate with nephropathy in Nigerians, as in African Americans.(14)

In addition to higher rates of ESKD, African Americans also have decreased allograft survival after kidney transplantation.(3) Based on UNOS data from 1994 to 2002, Hwang *et al.* reported a relative risk of 1.93 for graft loss after 3 months of transplantation in African American children compared to non-African American children.(15) Furthermore, kidneys donated by African Americans have significantly shorter graft survival compared to kidneys donated by European Americans.(16) This effect persists regardless of recipient race.(17)

Recent research indicates donor *APOL1* variants likely explain ethnicity-driven differences in kidney transplant outcomes.(18) Reeves-Daniel *et al.* investigated the relationship between donor *APOL1* risk variants and allograft survival after DDKT. This study included 136 African American donor kidneys from 106 deceased donors, along with their respective recipients (approximately 50% of recipients were African American). Kidneys from donors with 2 *APOL1* risk alleles had significantly shorter allograft survival relative to donors with 0/1 risk allele. In fact, African American donors without 2 *APOL1* risk variants had similar long-term graft survival as kidneys from European American donors. Differences in allograft survival based on *APOL1* genotype distributions were evident after approximately 20 months. Of grafts lost with 2 *APOL1* risk variants, 75% had biopsy-proven *APOL1*-associated lesions including FSGS and /or arteriosclerosis, compared to 11.8% among grafts lost with 0/1 *APOL1* risk alleles. Remarkably, the presence of 2 donor *APOL1* risk alleles had a more significant effect on allograft survival than did traditional risk factors such as degree of HLA mismatch, cold ischemia time, and expanded criteria donation. (18) It remains important that these results be replicated at other centers before considering widespread *APOL1* genotyping in African ancestry deceased donor kidneys.

In contrast to donor genotypes, recipient *APOL1* genotypes do not appear to impact allograft outcomes.(19) Lee and colleagues investigated the impact of recipient *APOL1* genotypes on allograft survival in 119 African American recipients. Approximately 38% of respective donors were African American. No difference in allograft survival was evident at 5 years between recipients carrying either 2 *APOL1* risk alleles versus 0 or 1. As genotype data on donors was unavailable, they performed a subgroup analysis including only non-African American donors and African American recipients. Again, no impact of *APOL1* recipient genotypes was detected on long term graft survival.(19)

The mechanism(s) by which *APOL1* risk variants cause FSGS, renal microvascular and interstitial disease in native kidneys and renal allografts are unknown. ApoL1 protein is predominantly synthesized in the liver and circulates in association with plasma high-density lipoprotein (HDL) cholesterol.(20) Madhavan *et al.* performed immunohistology and demonstrated that ApoL1 protein is present in podocytes, proximal tubules and the vascular endothelium of normal kidneys.(21) In cases of FSGS and HIVAN, the number of podocytes

containing ApoL1 was diminished and *de novo* ApoL1 appeared in the media of smooth muscle cells in medium sized arteries and arterioles. The authors suggested that ApoL1 may be endogenously synthesized by the kidney contributing to disease pathogenesis, or it may act in concert with uptake of extracellular ApoL1 protein.(21)

The functional role of ApoL1 in the kidney is unknown. Clinically, all individuals carrying 2 *APOL1* risk variants will not develop ESKD. Therefore, either gene-gene and/or gene-environment interactions appear important for disease initiation and nephropathy progression.(22, 23) As it has been shown that donor *APOL1* genotypes, not recipient genotypes, impact renal allograft survival, we postulate that high risk kidney donors may have had occult (subclinical) nephropathy at the time of donation, which when coupled with environmental stressors related to transplantation (prolonged cold ischemia time, CNIs, and/or viral infections with a renal reservoir) could accelerate disease. It is also possible that inflammatory mediators associated with transplantation may induce *APOL1* expression in donor kidneys; in the presence of risk variants this could lead to *APOL1*-associated nephropathy.(18, 19, 21, 24, 25)

Further insights into the mechanisms of *APOL1*-associated nephropathy may provide exciting opportunities to alter the significantly decreased long term graft survival seen with *APOL1* donor kidneys containing 2 risk variants.(18) HIV is an important environmental factor that dramatically increases the likelihood of developing *APOL1* associated HIVAN. Since the introduction of highly active anti-retroviral therapy (HAART), the incidence rate of HIVAN has sharply decreased in African Americans. Hence treating an environmental exposure (for example, viral infections like HIV) has potential to reduce rates of a genetically mediated kidney disease. As other interactive environmental factors (and interactive gene variants) are identified there will be the potential to alter the recipient milieu and prevent or ameliorate *APOL1*-associated kidney disease that results from the donor kidney.(23, 26)

Cohen *et al.* feel that genotyping African ancestry living kidney donors for presence of *APOL1* risk variants would be informative to them and potentially to recipients of their kidneys.(4) We will strongly advocate for deceased donor genotyping for *APOL1* in those with African ancestry upon replication of the findings from our single center study. *APOL1* genotyping may also allow clinicians to counsel potential African American living donors regarding their subsequent post-donation risk for ESKD. It is unknown whether living kidney donation in individuals carrying 2 *APOL1* risk alleles would precipitate or accelerates *APOL1*-associated nephropathy in the donors; these studies remain critical to perform. However, living kidney donors of African ancestry, compared to European, are known to face higher risk for post-donation ESKD, although overall rates are low and the higher risk in African Americans parallels that seen in the general population.(27, 28) This remains an important area of research. From the recipient perspective it is likely that donor *APOL1* genotyping may allow for better matching of recipient life expectancy and expected graft survival. Similar in concept to ECD kidneys, donor *APOL1* genotyping would allow for optimization of kidney allocation, moving the high risk *APOL1* 2 risk variant kidneys away from younger recipients with longer estimated post-transplant life expectancy.

Caveolin-1 gene (CAV1)

Caveolin-1 participates in transforming growth factor- β (TGF- β) receptor degradation and may limit the propagation of pro-fibrotic TGF- β signals.(29) Idiopathic pulmonary fibrosis and systemic sclerosis are fibrosing conditions shown to have decreased *CAV1* expression in affected organs.(30) *CAV1* expression also appears to play a role in other fibrosing kidney disorders. Park *et al.* showed that the degree of renal fibrosis in a mouse model of transient unilateral ureteral obstruction was inversely related to *CAV1* gene expression.(31) *CAV1* deficient mice had significantly greater renal fibrosis than did wild type mice and wild type animals developed more renal fibrosis than did mice overexpressing *CAV1*.

After kidney transplantation, interstitial fibrosis is one of the most common causes of allograft failure. Excluding kidneys lost to primary non-function or recipient death with a functioning graft, El-Zoghby *et al.* reported that approximately 30% of 1,317 transplanted kidneys in their series failed due to progressive interstitial fibrosis and tubular atrophy (IF/TA).(32) Among allografts that survived longer than 5 years, approximately 45% were eventually lost due to IF/TA.

Moore *et al.* investigated the relationship between kidney transplant outcomes, interstitial fibrosis and donor and recipient *CAV1* gene polymorphisms.(33) Their initial study (discovery sample) was conducted in England and included 785 living and deceased kidney donors with corresponding transplant recipients. All donors were of European ancestry, although 77.8% of recipients were European, 5.5% of African ancestry, 16.3% South Asian, and 0.4 % classified as “other”. Univariable and multiple regression analyses adjusting for traditional risk factors for graft loss detected a significantly increased risk for graft loss after 54 months of follow-up among those with donor AA genotypes (“A” denotes the *CAV1* risk variant), compared to donor non-AA genotypes. Furthermore, 59% of graft failures in the donor AA genotype group were due to biopsy proven interstitial fibrosis as the predominating lesion, relative to 26% in the donor non-AA genotype group. Other causes of graft loss were similar between donor AA and non-AA genotype groups. The investigators successfully replicated these results in a second study conducted in Ireland. Here, 679 deceased kidney donors and their respective recipients were evaluated. All donors and recipients in the replication sample were of European ancestry and donor AA genotype kidneys again conferred a statistically significant increased risk of graft loss, relative to donor non-AA genotype kidneys. It remains important to consider geographic and ethnic variation in the effects of *CAV1* (and other genes) on transplant outcomes; effects of this gene outside of UK and Irish populations remain to be reported and will need to be considered before general application.

Conflicting results were seen with regard to the effects of recipient *CAV1* genotype on long term allograft survival. In the English discovery sample, recipient *CAV1* genotypes had no impact on long term graft outcomes. However, in the Irish replication sample, recipient AA genotypes were associated with significantly higher risk of graft loss. Overall, no conclusions could be drawn with respect to recipient *CAV1* genotype on risk of graft loss. (33) The mechanism(s) by which donor *CAV1* AA genotypes confer a higher risk of renal graft loss remain to be determined and were not addressed in this report. Caveolin-1 forms

the backbone of caveolae, cell surface invaginations that play critical roles in cell signaling via endocytosis of a variety of toxins, enzymes, and receptors.(29, 34–39) Caveolin-1 decreases signal transduction of TGF- β by inducing endocytosis of the TGF- β receptor.(29) TGF- β plays a key role in activating pathways which may ultimately lead to fibrosis in the renal allograft.(40–43) An attractive, but speculative mechanistic model to explain the findings of Moore *et al.* (33) includes alterations in donor kidney *CAVI* expression level or morphologic variation of caveolin-1 due to gene polymorphisms that limit the ability of the structural protein to attenuate the pro-fibrotic TGF- β signal. This would lead to accelerated interstitial fibrosis and shorter allograft survival.

Another aspect of *CAVI* relevant to kidney transplantation is its role in BK polyoma virus-associated nephropathy. BK virus is typically acquired during childhood and remains latent in cells of the kidney and uroepithelium. With immunosuppression, BK virus may enter a replicative phase producing allograft nephritis with the potential for graft failure. Moriyama *et al.* reported replicating BK virus enters nearby uninfected human renal proximal tubule cells through caveolar endocytosis.(44) In the report by Moore *et al.* evaluating *CAVI*, the relationship between *CAVI* gene polymorphisms and likelihood of developing BK virus nephropathy was not specifically investigated.(33) This remains an important avenue for future research.

Future implications related to donor *CAVI* genotyping for clinicians include the potential to modify environmental factors which may act synergistically to promote allograft fibrosis. It is tempting to speculate that deceased donor kidneys with the high risk *CAVI* AA genotype could have improved allograft survival with decreased cold ischemia times or CNI-free immunosuppression; although this remains to be evaluated. In other *CAVI*-associated fibrosing diseases, increasing the bioavailability of caveolin-1 via genetically engineered vectors may decrease subsequent degrees of fibrosis.(30, 31) This may prove to be a potential therapeutic approach for recipients of *CAVI* AA risk genotype donor kidneys. Finally, if relationships exist between *CAVI* genotype and susceptibility to BK virus nephropathy, perhaps reductions in the intensity of immune suppression based on this genotypic information could ameliorate disease risk.

Multi-drug resistance 1 encoding P-glycoprotein gene (*ABCB1*)

Tacrolimus is included in the initial maintenance immunosuppression regimens in 94% of pediatric kidney transplant recipients.(3) One year kidney allograft survival rates have significantly improved with the introduction of CNIs, an effect attributed to reductions in acute rejection episodes with these more potent immunosuppressive medications.(45–47) However, CNIs are nephrotoxic and can contribute to long-term renal graft loss.(48) There is a direct correlation between serum CNI concentrations and anti-rejection effect, as well as nephrotoxicity. This results in a narrow therapeutic window.(49–52) However, even in the setting of careful CNI drug monitoring there appear to be significant inter-individual differences in time to development of CNI-related nephrotoxicity and subsequent progression to ESKD. Genetic polymorphisms relating to CNI pharmacokinetics and pharmacodynamics have received attention as potential mediators of the inter-individual

differences in CNI levels and effect, particularly *ABCB1* encoding the drug transporter P-glycoprotein.

Woillard *et al.* first investigated the relationship between donor and recipient *ABCB1* C3435T polymorphisms (single nucleotide polymorphism [SNP] rs1045642) and renal allograft survival in a study investigating 227 French deceased donors and their recipients. (53) They found that donor *ABCB1* “TT” variants were associated with a significantly increased risk of graft loss after mean follow-up of 72 months. Recipient *ABCB1* genotypes did not appear to impact allograft survival.

Moore *et al.* (54) subsequently examined *ABCB1* donor genotypes for effects on allograft survival in three distinct cohorts including nearly 4,500 kidney transplants. The initial sample consisted of 811 living and deceased kidney donors with their recipients from England. As in their report evaluating *CAVI*, 82.1% of recipients were European, 5.5% of African ancestry, and 16.3% South Asian; 100 % of kidney donors were European. Recipients were uniformly maintained on cyclosporine. Recipients receiving a kidney from a donor with the *ABCB1* “CC” genotype (C denotes an allele known to alter protein expression) had statistically significant higher rates of graft failure compared to those who received a kidney from a non-CC donor. These results directly conflict with those of Woillard *et al.* (53) Moore and colleagues then validated their results in two replication samples. (54) The first was from Ireland and included 675 European deceased donors and their respective recipients (99% of recipients were European). In this first validation study, 82.5% of recipients received cyclosporine and 17.5% tacrolimus. Again recipients receiving a kidney from a donor with the *ABCB1* CC genotype had statistically significant higher rates of graft failure relative to those receiving a non-CC donor genotype kidney.

Moore *et al.* (54) attempted further replication between donor *ABCB1* genotypes and kidney transplant outcomes in the Collaborative Transplant Study (CTS). The CTS cohort included 2,985 North American and European kidney donors with their recipients; 100% of donors and recipients were of European ancestry. In the CTS, 84.8% of transplant recipients were treated with cyclosporine and 15.2 % tacrolimus. No significant relationship was identified between donor *ABCB1* genotypes and death-censored graft survival in the overall CTS cohort. Heterogeneity of CTS study populations, with patients from different countries and centers using different protocols may have contributed. However, in the subgroup of 452 recipients maintained on tacrolimus maintenance immunosuppression there was a statistically significant increased risk of graft loss in recipients of a kidney from a donor with the *ABCB1* CC genotype, compared to those receiving a kidney from a donor with a non-CC genotype. In the three cohorts assessed by Moore *et al.*, associations were not observed between recipient *ABCB1* genotypes and renal graft survival. (54)

The mechanism by which donor *ABCB1* genotypes increase the risk for graft loss remains unclear; neither the Woillard *et al.* (53) or Moore *et al.* (54) report listed causes of graft loss. P-glycoprotein, the gene product of *ABCB1*, is a transmembrane protein that actively transports CNIs from the intracellular to the extracellular compartment. (55, 56) P-glycoprotein is expressed in a variety of cells including renal proximal tubule cells. (57) Although both Woillard and colleagues and Moore and colleagues found that donor *ABCB1*

C3435T polymorphisms were associated with increased risk for renal allograft loss, the associated risk variants differed.(53, 54) The study by Moore *et al.* (54) found consistent evidence of association between donor *ABCB1* CC genotypes and outcomes and was by far the larger study with two large validation samples.(54) The authors proposed that increased P-glycoprotein expression with the CC genotype might result in increased cell growth, anti-apoptotic effects on fibroblasts, promotion of cholesterol-ester mediated vascular damage, and increased propensity to ischemia-related injury as observed in animal models. Further, liver transplant recipients possessing the *ABCB1* CC genotype had higher rates of post-transplant CKD.

It remains unclear why different *ABCB1* C3435T polymorphisms are associated with increased allograft loss in the two reports.(53, 54) Neither study could account for potential gene-gene interactions relating to CNI pharmacokinetics and/or pharmacodynamics which could have influenced results. Furthermore, unaccounted environmental factors or recipient characteristics may explain the discordant results. As kidney donor *ABCB1* CC genotypes more consistently demonstrated effects on renal allograft survival in the larger study (54), future implications for transplant physicians may include selective use of CNI-free maintenance immunosuppression regimens to overcome the potential effects of donor-associated risk variants. We add that *ABCB1* gene polymorphisms do not appear to significantly impact acute rejection, delayed graft function, or serum creatinine concentration after kidney transplantation. (58–60)

Conclusions

The current era of genomic medicine holds tremendous promise for improving outcomes in patients with ESKD who require kidney transplantation. It is particularly important that durable allograft survival from a first kidney transplant be achieved in pediatric, adolescent and young adults with ESKD, particularly those with renal-limited disorders. These individuals have the best potential for long term survival and are less likely to succumb with a functioning graft, relative to adult or elderly patients with systemic diseases such as diabetes mellitus. Much of the benefit from living related donation and six antigen HLA matched deceased donor kidneys comes from associated lower rejection rates and need for lower doses of immunosuppression. We feel that the ongoing relative shortage of live kidney donors and use of more potent immunosuppression (with lesser emphasis on HLA matching) makes the effects of genetic polymorphisms that are present in donor transplant kidneys important to consider in the process of organ allocation. Laboratories can rapidly genotype deceased donors for the presence of risk variants in the *APOL1*, *CAVI*, *ABCB1* and other genes as they are identified in the future. These variants may impact allograft survival and/or metabolism of immunosuppressants. Nearly 50% of deceased donor kidneys harboring 2 *APOL1* nephropathy risk variants will fail three years post-transplant.

We feel it is critically important that studies of kidney transplant outcomes include assessments of donor nephropathy risk variants and drug metabolism/pharmacogenomics. The best hope for long term renal allograft survival will include transplanting kidneys with the fewest number of nephropathy risk variants, as well as optimizing potentially interactive environmental factors, such as reducing cold ischemia time and appropriately dosing

immunosuppression to match the risk of rejection, interstitial fibrosis, and the transplanted kidney's ability to metabolize these medications.

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Table 1

Donor kidney gene variants implicated in renal transplant allograft survival

Gene	Author	Total n	Chromosomal location	Risk variant	Hazard Ratio for graft loss
<i>APOLI</i>	Reeves-Daniel et al. (18)	136	22q13.1	G1,G2 (recessive)	3.84
<i>CAVI</i>	Moore et al. (33)	Discovery 785	7q31.1	AA (recessive)	1.97
		Replication 697			1.56
<i>ABCB1</i>	Moore et al. (54)	Discovery 811	7q21.12	CC (recessive)	1.69
		Replication 675			1.68
		CTS subgroup 452			1.84
	Woillard et al. (53)	227		TT	9.346