Deceased donor multidrug resistance protein 1 and caveolin 1 gene variants may influence allograft survival in kidney transplantation

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Variants in donor multidrug resistance protein 1 (*ABCB1*) and caveolin 1 (*CAV1*) genes are associated with renal allograft failure after transplantation in Europeans. Here we assessed transplantation outcomes of kidneys from 368 African American (AA) and 314 European American (EA) deceased donors based on 38 single-nucleotide polymorphisms (SNPs) spanning *ABCB1* and 16 SNPs spanning *CAV1*, including previously associated index and haplotype-tagging SNPs. Tests for association with time to allograft failure were performed for the 1233 resultant kidney transplantations, adjusting for recipient age, sex, ethnicity, cold ischemia time, panel reactive antibody, human leukocyte antigen match, expanded-criteria donation, and *APOL1*-nephropathy variants in AA donors. Interaction analyses between *APOL1* with *ABCB1* and *CAV1* were performed. In a meta-analysis of all transplantations, *ABCB1* index SNP rs1045642 was associated with time to allograft failure and other *ABCB1* SNPs were nominally associated, but not *CAV1* SNPs. *ABCB1* SNP rs1045642 showed consistent effects with the 558 transplantations from EA donors, but not with the 675 transplantations from AA donors. *ABCB1* SNP rs956825 and *CAV1* SNP rs6466583 interacted with *APOL1* in transplants from AA donors. Thus, the T allele at *ABCB1* rs1045642 is associated with shorter renal allograft survival for kidneys from American donors. Interactions between *ABCB1* and *CAV1* with *APOL1* may influence allograft failure for transplanted kidneys from AA donors.

Kidney International advance online publication, 8 April 2015; doi:10.1038/ki.2015.105

KEYWORDS: *ABCB1*; African American; allograft failure; *APOL1*; *CAV1*; kidney transplantation

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Received 28 October 2014; revised 2 February 2015; accepted 19 February 2015

Genetic variations in organ donors and recipients have the potential to impact outcomes after transplantation.[1] In Europeans, variations in the donor multidrug resistance protein 1 (*ABCB1*) and caveolin 1 (*CAV1*) genes are associated with kidney allograft survival.[2–5] In a similar manner, the G1 and G2 coding variants in the powerful *apolipoprotein L1* gene (*APOL1*) have marked effects on time to renal allograft failure after transplantation from African American (AA) deceased donors,[6,7] and variants in *SHROOM3* predispose to renal allograft fibrosis.[8] In contrast, variation in *APOL1* in recipients of kidney transplants does not impact outcomes.[9] *APOL1* G1 and G2 nephropathy-risk variants are virtually limited to populations with recent African ancestry. These variants produce ethnic-specific risk, as they are nearly absent in individuals with European, Hispanic, and Asian ancestry.[10]

On the basis of the potential for ethnic-specific differences in risk allele frequencies, it is important to validate the effects of kidney-donor gene variants possibly affecting allograft survival in members of different racial/ethnic groups.[11] Assessment of variation along the full length of implicated genes is also required due to ancestry-specific haplotype block structures and to further refine the position of potential functional variants. Testing a single, previously associated, index genetic variant may be insufficient for full interrogation of effects of that gene on transplant outcomes in other ethnic groups. The present report assessed effects of variation in the *ABCB1* and *CAV1* genes of deceased European American (EA) and AA kidney donors on transplant outcomes. Haplotype-tagging single-nucleotide polymorphisms (htSNPs) spanning these genes were evaluated and genetic association analyses for time to renal allograft failure were performed for the resultant transplantations. Adjustment was done for the impact of *APOL1* risk variants, and interactions between *ABCB1* and *CAV1* htSNPS with *APOL1* were tested.

RESULTS

The genetic association analyses for 675 kidney transplantations from AA donors were based on the results of two kidneys from the same donor separately engrafted in 102 Alabama and 205 North Carolina transplantations and one kidney engrafted from 17 Alabama and 44 North Carolina donors. Eight kidney transplantations were performed before 2001, 86 from 2001 to 2006, 397 from 2006 to 2010, and 184 after 2010. The median (first quartile, third quartile) follow-up duration after engraftment was 34.3 months (13.8, 57.9 months). Table 1 lists demographic characteristics of transplant recipients (57.8% of whom were African Americans) and of AA deceased organ donors. Median donor and recipient ages were 37.0 and 50.0 years, respectively; 59.2% of donors and 58.4% of recipients were male. Median terminal serum creatinine concentration was 1.1 mg/dl, peak panel reactive antibody (PRA) titer 5%, cold ischemia time 22.0 hours, and number of human leukocyte antigen (HLA) mismatches 5. Peak PRA titers exceeded 20% in 31.7, 34.1, and 31.9% of the recipients of Alabama AA, North Carolina AA, and North Carolina EA kidneys, respectively ($P = 0.71$); induction immunosuppression was administered to 92.3, 89.7, and 92.7% of recipients of Alabama AA, North Carolina AA, and North Carolina EA kidneys, respectively ($P = 0.29$).

The genetic association analyses for 558 kidney transplantations from EA donors were based on the results of two kidneys from the same donor separately engrafted in 244 North Carolina transplantations and one kidney engrafted from 70 North Carolina donors; 270 transplantations were performed from 2006 to 2010 and 288 after 2010. The median (first quartile, third quartile) follow-up duration after engraftment was 23.7 months (12.1, 33.9 months). Table 2 lists demographic characteristics of transplant recipients (42.3% of whom were African Americans) and of EA deceased organ donors. Median donor and recipient ages were 44.0 and 55.0 years, respectively; 60.5% of donors and 55.2% of recipients were male. Median terminal serum creatinine concentration was 0.9 mg/dl, peak PRA 6%, cold ischemia time 23.0 hours, and number of HLA mismatches 4. Immunosuppression varied by center, but generally included antibody induction with a calcineurin inhibitor (CNI) and an antiproliferative agent, with or without corticosteroids.

In the meta-analysis of 1233 transplantations from all deceased AA and EA kidney donors, no SNPs in *CAV1*, including the previously associated index SNP rs4730751, met statistical significance for association with time to renal allograft failure in the fully adjusted model that accounted for donor *APOL1* risk status in the AA subset and recipient, age,

Table 1 | Demographic data for 368 African American kidney donors and 675 resultant transplantations

Donor characteristics ($N = 368$)						
Categorical variables		*N*			%	
Donor gender (% male)		218			59.2%	
Standard criteria donor (%)		296			80.4%	
Continuous variables	*N*	1st Quartile	Median	Mean	s.d.	3rd Quartile
Donor age (years)	368	20.0	37.0	35.3	17.5	50.0
Donor terminal serum creatinine (mg/dl)	300	0.85	1.1	1.2	0.7	1.5
Recipient characteristics ($N = 675$)						
Categorical variables		*N*			%	
Recipient gender (% male)		394			58.4%	
Recipient ethnicity (% African American)		390			57.8%	
Allograft failure (%)		117			17.3%	
Continuous variables	*N*	1st Quartile	Median	Mean	s.d.	3rd Quartile
Peak PRA (%)	674	0.0	5.0	23.8	32.8	38.0
Recipient age (years)	675	38.0	50.0	47.8	15.6	60.0
Recipient body mass index (kg/m^2)	621	23.6	26.9	27.6	5.7	31.4
Cold ischemia time (hours)	641	16.1	22.0	23.5	11.2	28.3
HLA mismatch (#)	675	4.0	5.0	4.3	1.4	5.0
Duration of transplant follow-up (months)	675	13.8	34.3	39.5	30.1	57.9

Abbreviations: HLA, human leukocyte antigen; PRA, panel reactive antibody.