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Analysis of 75 Candidate SNPs Associated with Acute Rejection in Kidney Transplant Recipients: Validation of rs2910164 in MicroRNA *MIR146A*

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

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Background: Identifying kidney allograft recipients who are predisposed to acute rejection (AR) could allow for optimization of clinical treatment to avoid rejection and prolong graft survival. It has been hypothesized that part of this predisposition is caused by the inheritance of specific genetic variants. There are many publications reporting a statistically significant association between a genetic variant, usually in the form of a single nucleotide polymorphism (SNP), and AR. However, there are additional publications reporting a lack of this association when a different cohort of recipients is analyzed for the same SNP.

Methods: In this report we attempted to validate 75 common genetic variants, which have been previously reported to be associated with AR, using a large kidney allograft recipient cohort of 2,390 European-Americans and 482 African Americans.

Results: Of those variants tested, only one variant, rs2910164, which alters expression of the microRNA *MIR146A*, was found to exhibit a significant association within the African American cohort. Suggestive variants were found in the genes *CTLA* and *TLR4*.

Discussion: Our results show that most variants previously reported to be associated with AR were not validated in our cohort. This shows the importance of validation when reporting associations with complex clinical outcomes such as AR. Additional work will need to be done to understand the role of MIR146A in the risk of AR in kidney allograft recipients.

Keywords

Acute rejection; single nucleotide polymorphisms; SNPs; kidney; transplant; graft dysfunction

Introduction

Kidney allograft transplantation is the treatment of choice for end-stage kidney disease. Unfortunately, graft function decreases with the occurrence of chronic rejection (interstitial fibrosis/tubular atrophy; IF/TA). Acute rejection (AR) is a major risk factor for IF/TA and associated graft loss in kidney allograft recipients (1–3), particularly when renal function does not return to baseline. Clinical care of kidney allograft recipients could be greatly improved if individuals at risk for AR could be identified before transplantation, allowing for better individualized clinical care. AR is a complex event with several different presentations including early and late AR, antibody-mediated rejection (ABMR) and T cell-mediated rejection (TCMR). Classification of AR is continually being updated based on new and emerging techniques in histopathology, based in part on the integration of new genetic biomarkers (4, 5). It has been hypothesized that some individuals have increased risk for AR due to the inheritance of specific genetic variants (6). To understand the impact of genetic variation on AR, numerous studies in the last several decades have been undertaken to identify genetic variants associated with AR (7–70). Table 1 shows 75 genetic variants, as single nucleotide polymorphisms (SNPs), previously reported to be associated with AR. Unfortunately, there are also many reports showing failed attempts to validate some of these variants (53, 71, 72).

In this report, we attempted to validate 75 variants previously reported in the literature to be associated with AR using DNA from combing two multicenter cohorts of kidney allograft recipients enrolled in genome-wide association studies (GWAS). The sample size of these

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two cohorts combined is larger than most of the previous studies and the candidate-SNP approach instead of a genome-wide analysis can maximize our power to validate previous findings.

Materials and Methods

The design of the Deterioration of Kidney Allograft Function (DeKAF) Genomics and the Genomics of Transplantation (GEN-03) cohorts along with each participant's characteristics has been previously reported (73–75). For this analysis, the DeKAF Genomics and the GEN-03 studies were combined and the kidney transplant recipients with GWAS data were identified and divided into two sub-cohorts consisting of 2,390 European-Americans (EA) and 482 African Americans (AA) kidney allograft recipients and tested separately. Though self-reported race was available in the clinical information, subjects were separated into EA and AA sub-cohorts based on ancestry principal components. Subjects were enrolled at time of transplant and signed informed consents were approved by the Institutional Review Boards of the enrolling centers. This study is registered at www.clinicaltrials.gov (and).

Clinical information was obtained from the respective medical records (74, 75). Induction therapy was administered as per transplant center preference but mainly consisted of rabbit anti-thymocyte globulin (rATG), basiliximab or Campath-1H. Immunologically high-risk patients were more likely to receive rATG, such as those with donor specific antibody, pregnancies, or repeat transplants. AR was defined as time to first T-cell, antibody mediated, or mixed T-cell and antibody mediated rejection post-transplant as determined by the enrolling center and treating physician. Rejection was biopsy confirmed in 96% of the cases. The median time to first 12 month AR was 53 days and the median time to first all-time AR was 105.5 days. Both first 12 month AR and all time AR were used in the analysis.

Papers evaluating genetic variants associated with AR were identified through Pubmed. Variants which were shown to have a statistically significant association (p-value <0.05) with AR in solid organ transplantation patients were included in this study (6). The variants which were chosen from the literature for validation in this report are shown in Table 1. All but 6 variants were reported in studies using cohorts of kidney allograft recipients. Those six SNPs not identified in kidney recipients were reported in liver allograft recipients (rs9296068 in HLA-DOA; rs1063320 in HLA-G; rs1800796 in IL6; rs3757385 in IRF5; rs2476601 in PTPN22; rs3775291 in TLR3). Genotype information for this study was extracted from our previous study using a custom genome-wide Affymetrix Axiom Transplant Array chip created specifically for analysis of allograft recipients (71, 76). The 75 variants analyzed are located in 58 genes. For those variants which were not part of the GWAS chip, a proxy SNP was selected which was present on the chip and where genotypes were available. In all cases, the r^2 between the reported variant and the proxy SNP was 1.0 as determined by the SNP Annotation and Proxy Search program (SNAP) (77). All selected SNPs were tested for Hardy-Weinberg Equilibrium (HWE). SNPs with a HWE test p-value <0.001 or sample missing rate > 1% were replaced by imputation using the IMPUTE2 program (78). The imputation quality (info) score were above 0.95 for all but two SNPs (rs2426295 and rs2430561, info ~ 0.7 and 0.8, respectively).

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Differences in baseline characteristics of recipients without AR vs. with AR were tested using t-tests for continuous variables and chi-sq tests for categorical variables.

Cox proportional-hazard models were used to test the association between each literature identified SNP and time to first AR per person in our cohort. SNPs were coded using an additive genetic model, *i.e.*, the number of copies of a reference allele. The at-risk time period began on the day of transplant and lasted until the earliest event of AR, death, graft failure, last date of follow up, or common close out date. For the outcome of AR in the first 12 months post-transplant, an additional censoring date of one year post-transplant was added. When testing a single SNP association, we stratified by transplant center, and adjusted for variables determined using model selection. We performed backwards model selection with a retention p-value of 0.10 on the outcome of all time AR, separately for AA and EA cohorts, using all of the variables listed in Table 2. For the EA cohort, the retained variables were: gender, primary cause of ESRD, need for dialysis in the first 14 days post-transplant, T- or B-cell crossmatch positive, plasmapheresis prior to transplant, greater than zero HLA mismatches, type of antibody induction, calcineurin inhibitor type at transplant, age at transplant, and donor age. For the AA cohort, the retained variables were: greater than zero % panel reactive antibodies, T- or B-cell crossmatch positive, plasmapheresis prior to transplant, smoking status, calcineurin inhibitor type at transplant, and SPK. Significance for an association between a SNP and AR was set at $p<6.6\times10^{-4}$ (Bonferroni correction with 75 independent tests). Analyses were conducted using SAS v9.4 (The SAS Institute, Cary, NC, USA, http://www.sas.com).

Single SNP Cox proportional hazard models were used to the analysis of variants associated with time to death-censored chronic graft failure (DCGF). Backward selection with a retention p-value of 0.10 was performed separately for European-American and African-American cohorts. In the European-American cohort (DCGF events = 273), models were adjusted for gender, primary cause of ESRD, need for dialysis, cross T- or B-cell match, plasmapheresis prior to transplant, HLA mismatches, type of antibody induction, CNI at baseline, age and donor age. In the African-American cohort (DCGF events = 105), models were adjusted for PRA positive, cross T- or B-cell match, plasmapheresis prior to transplant, smoking status, CNI at baseline and SPK. Both cohorts were stratified by transplant center.

Results

Characteristics of the two cohorts are shown in Table 2. Significant differences ($p<0.002$) between recipients with and without AR for the EA cohort are, mean age at enrollment in years ($p=0.0004$), mean donor age in years ($p=0.0014$), plasmapheresis prior to transplant ($p<0.0001$), HLA mismatches ($p<0.0001$), type of antibody induction ($p<0.0001$) and calcineurin inhibitor type ($p<0.001$). Significant differences between recipients with and without AR for the AA cohort are, panel reactive antibodies ($p=0.002$), T or B cell crossmatch (0.0013), plasmapheresis prior to transplant ($p<0.0013$), and calcineurin inhibitor type at time of transplant ($p<0.0002$).

The results of the association analysis for the SNPs tested are found in Table 3. The only significant SNP was rs2961920 ($p=1.1\times10^{-4}$), a proxy for rs2910164, which is located in the

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MIR146A gene. This SNP was only significant in the AA cohort for all-time AR. The variant was also marginally significant ($p=1.9\times10^{-3}$) for AR within 12 months. The hazard ratio (95% CI) for this variant for AR within 12 months was 2.28 (1.42–3.89) and for AR all time was 2.43 (1.50–3.48). A Kaplan-Meier analysis for AR by MIR146A genotype is shown in Figure 1. At 28 months, 85% of recipients heterozygous for the risk allele (C/A) were AR free whereas individuals homozygous for the risk allele (A/A), at 28 months, only 75% were AR free. This variant was not significant in the EA cohort (p=0.59; 12 months AR and p=0.45; all time AR).

There were two suggestive variants. In the EA cohort, SNP rs5742909 (p=0.0049; 12 months AR and p=0.012; all time AR) within the *CTLA4* gene and in the AA cohort, SNP rs10759932 (p=0.0089; 12 months AR and p=0.0046; all time AR) within the *TLR4* gene. All other tested variants were not significant ($p > 0.02$).

All variants were also tested against time to death-censored graft function (DCGF) using a Cox proportional hazard model (Table 1S). There were no significant associations with any of the variants, but suggestive associations were found in the AA cohort for SNP rs61527852 in the IL3 gene (p=0.0087; all time AR) and for SNP rs2961920 in the MIR146A locus in both the EA cohort (p=0.0046; all time AR) and the AA cohort but less significant (p=0.049; all time AR)

Discussion

Since the beginning of kidney allograft transplantation, there has been considerable reduction in occurrence of AR and improved treatments, resulting in an almost 95% graft survival rates for the first year after transplantation. Unfortunately, there remains an insidious rate of late graft dysfunction and loss and one of the major clinical problems in transplantation. The risk of graft loss has been shown to be increased in the event of AR (1). Being able to reduce AR events would improve graft survival. It has been hypothesized that some recipients are genetically predisposed to increased risk for AR (6, 79). Those genetic variants with the greatest impact on AR are within the human leukocyte antigens (HLA) related loci within the major histocompatibility complex (MHC) (80). HLA alleles are strong predictors of AR and matching HLA alleles between the recipient and donor organ greatly decreases the risk for AR. Though the HLA loci plays an important role in AR, other genes which impact the immune system also have genetic variation and these alleles may also impact AR risk. To this end, many variants within these genes have been reported for their association with AR.

In this analysis, 75 SNPs, previously reported to be associated with the risk of AR, were tested in our EA and AA cohorts of kidney allograft recipients. Only one of these SNPs was found to be significant; A SNP within the microRNA 146a in the AA cohort. In a previous report it was found that rs2910164 in the *MIR146A* gene was associated with lowest overall survival among 350 North Indian renal allograft recipients and a three-fold higher risk for AR (70). The hazard ratio was similar to the previous report on this variant, 2.43 vs. 2.63. In the previous report, the recipients were from north India and in our analysis the recipients with the significant p-value were within the AA cohort. The EA cohort was not significant

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for this variant. We speculate that the lack of significance in the EA cohort may be the result of not having additional variants in other genes which were present in the north Indian and AA populations and act synergistically with rs2910164.

MIR146A has a number of targets, including mRNAs from genes involved in immune regulation including regulatory T-cells (81). An *in silico* analysis identified several target genes including an interleukin-1 receptor-associated kinase (*IRAK1*) gene, and TNF-receptor associated factor (*TRAF-6*) gene (70). MIR146A is thought to help modulate the immune system by suppressing inflammatory responses, in part through the NF-κB signaling pathway. The variant allele has been shown to reduce the expression of this microRNA, possibly resulting in an enhanced inflammatory response to the allograft, increasing the risk of AR (82, 83). This variant has also been reported to be associated with type 2 diabetes with increased fasting glucose and HbA1C levels and cardiovascular disease risk factors such as increased diastolic blood pressure and triglycerides (84).

The three variants which exhibited suggestive evidence for an association with AR included SNP rs5742909 within the cytotoxic T-lymphocyte associated protein 4 (*CTLA4)* gene and SNP rs10759932 within the toll like receptor 4 (*TLR4)* gene. The CTLA4 gene plays an inhibitory role in T-cell signaling and the TLR4 gene product is a lipopolysaccharide receptor and plays a fundamental role in pathogen recognition and activation of innate immunity (85, 86). We also tested all variants for their association with DCGF, but none were significant.

There are many reasons for the high number of variants that did not replicate in this study (87, 88). For the most part, most of the published studies are underpowered. An additional source of error in replication may be differences between populations and clinical care. Also, six of these variants were identified in liver recipients and may not be important in kidney allograft recipients. In this analysis, we used recipients from a single multicenter study in which identical clinical variables were collected for all individuals in the cohort. Many of the published studies analyzed only single univariate associations and did not adjust for clinical characteristics which can improve the power of statistical testing. Additionally, the follow-up period to AR is often too short to see an impact of the variant on AR risk and no consideration is given to linkage disequilibrium. Additional reasons have been stated in a report which attempted to identify donor specific variants associated with long- and short-term outcomes using a GWAS in renal allograft recipients (89). In this study a genome-wide association study was done on 2,094 renal transplant-pairs, but no variants outside of the HLA region were found to be statistically significant in a 5,866 replication cohort. The authors suggested that both phenotype heterogeneity and the lack of statistical power due to limited sample size is a possible cause of no statistically significant variants being identified. The AR phenotype is most likely both clinically and genetically heterogeneous making identification of associated variants unlikely unless larger populations are used.

Other variables which may impact AR and/or graft loss include subclinical rejection and immunosuppressant adherence. In both cases this information was not available from the published papers and we did not collect this data in our cohort so the inclusion of these

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variables in our analysis was not possible, though both of these have been shown to be important in rejection risk and health of the allograft (90, 91).

The positive association of the MIR146A with AR provides a novel pathway to study and may provide additional genes and their variants as candidates for recipient risk for AR and possible therapeutic targets to reduce this risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS PAGE

IF/TA	interstitial fibrosis/tubular atrophy
AR	acute rejection
ABMR	antibody-mediated rejection
TCMR	T cell-mediated rejection
SNPs	single nucleotide polymorphisms
GWAS	genome-wide association studies
DeKAF	Deterioration of Kidney Allograft Function
EA	European-Americans
AA	African Americans
rATG	rabbit anti-thymocyte
SNAP	SNP Annotation and Proxy Search program
HLA	human leukocyte antigens
MHC	major histocompatibility complex

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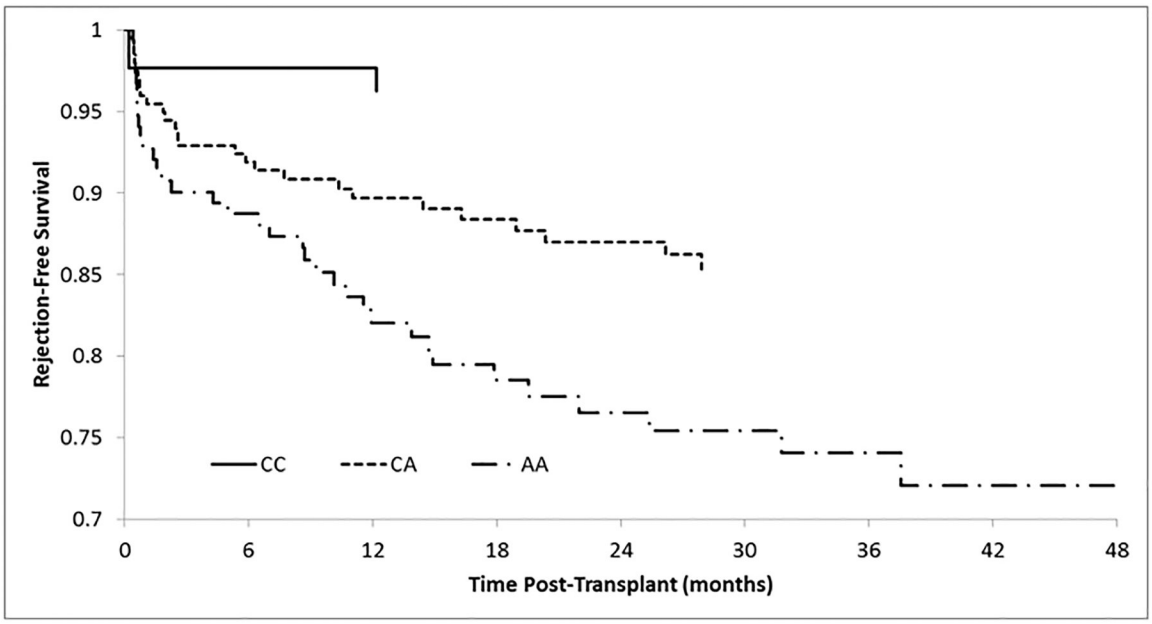

Figure 1. A Kaplan-Meier analysis of proxy SNP rs2910164 in *MIR146A* for acute rejection

A Kaplan-Meier analysis for rejection-free kidney recipients based on the genotypes of MIR146A. The solid line represents the CC genotype, dashed line represents the CA genotype and the dash-dot-dash line represents the AA genotype. The A allele was found to be associated with a greater risk of acute rejection.

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Table 1.

Candidate SNPs associated with acute rejection reported in the literature.

SNP rs#	Proxy†	Gene	Chrm	Position††	Nucleotide Change	Protein Change	Ref
rs2032582	rs4148738	ABCB1	7	87531302	c.2677T>G	p.Ser893Ala	7
rs2269475		AIF	6	31616154	c.43C>T	p.Arg15Trp	8
rs5186		AT1R	3	148742201	c.*86A>C	3’ UTR	9
rs10765602	rs55637918	DEUP1 (CCDC67)	11	93314999	g.93048165G>T	5’ of gene	10
rs1024611		CCL2	17	34252769	c.-2582A>G	5’ of gene	11
rs2107538		CCL5	17	35880776	c.-471G>A	5’ of gene	12
rs1799864		CCR2	3	46357717	c.190G>A	p.Val64Ile	13, 14
rs1799987		CCR5	3	46370444	c.-301+246A>G	Intronic	13, 14, 15
rs3116496	rs10490574	CD28	2	203729789	c.243+17T>C	Intronic	16, 17
rs1129055		CD86	3	122119472	c.592G>A	p.Ala198Thr	17
rs733618		CTLA4	2	203866221	c.-1722T>C	5’ of gene	18
rs5742909		CTLA4	2	203867624	c.-319C>T	5’ of gene	19, 20
rs231775		CTLA4	2	203867991	c.49A>G	p.Thr17Ala	21, 22 23, 24
rs3087243		CTLA4	2	203874196	c.1421G>A	3’ of gene	24
rs4073		CXCL8	4	73740307	c.-352A>T	5’ of gene	25
rs2515641		CYP2E1	10	133537858	c.1263C>G	p.Phe421 =	26
rs776746		CYP3A5	7	99672916	c.219–237G/A	Intronic	27
rs1042032	rs4149257	EPHX2	8	27544557	c.35A>G	3’ UTR	28
rs1799963		F2	11	46739505	c.97G>A	3’ UTR	29
rs6025		F5	1	169549811	c.1601G>A	p.Arg534Gln	29, 30
rs7851696		FCN2	9	134887245	c.772G>C	p.Ala258Ser	31
rs1801274		FCGR2A	1	161509955	c.500A>G	p.His166Arg	32
rs9296068		HLA-DOA	6	33020918	g.4470122T>G	5’ of gene	33
rs1063320		HLA-G	6	29830972	c.*233C>G	3’ UTR	34
rs5498		ICAM1	19	10285007	c.1405A>G	p.Lys469Glu	35
rs1143634		IL1B	2	112832813	c.315C>T	p.Phe105=	36
rs2069762		IL2	4	122456825	c.-385T>G	5’ of gene	37
rs228942		IL2RB	22	37128579	c.1173C>A	p.Asp391Glu	38

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SNP rs#	Proxy[†]	Gene	Chrm	Position[††]	Nucleotide Change	Protein Change	Ref
rs228953	rs2284033	IL2RB	22	37135396	c.750C>T	p.Gly250=	39
rs181781	rs657075	IL3	5	132059422	c.-1285G>A	5’ of gene	39
rs2073506	rs61527852	IL3	5	132059045	c.-1662C>A	5’ of gene	39
rs40401	rs31480	IL3	5	132060785	c.79C>T	p.Pro27Ser	39
rs2243250		IL4	5	132673462	c.-589C>T	5’ of gene	40
rs1801275		IL4R	16	27363079	c.1727A>G	p.Gln576Arg	41
rs1800796	rs1524107	IL6	7	22726627	c.-636G>C	5’ of gene	42
rs1800795		IL6	7	22727026	c.-237C>G	5’ of gene	43
rs1800896		IL10	1	206773552	c.-1117A>G	5’ of gene	44, 45
rs1800871		IL10	1	206773289	c.-854T>C	5’ of gene	44
rs1800872		IL10	1	206773062	c.-627A>C	5’ of gene	7, 44
rs763780		IL17F	6	52236941	c.482A>G	p.His161Arg	46
rs187238		IL18	11	112164265	c.-368G>C	5’ of gene	47
rs2278293		IMPDH1	7	128400698	c.579+119G>A	Intronic	48
rs2278294		IMPDH1	7	128400645	c.580–106G>A	Intronic	48
rs11706052		IMPDH2	3	49026677	c.819+10T>C	Intronic	7
rs2430561		INFG	12	68158742	c.115–483A>T	Intronic	49
rs3757385	rs3807307	IRF5	7	128937250	c.-811T>G	5’ of gene	50
rs5918		ITGB3	17	47283364	c.176T>C	p.Leu59Pro	51
rs7096206		MBL2	10	52771925	c.-290C>G	5’ of gene	52
rs5030737		MBL2	10	52771482	c.154C>	p.Arg52Cys	52
rs180045		MBL2	10	52771475	c.161G>A	p.Gly54Asp	52
rs1800451		MBL2	10	52771466	c.170G>A	p.Gly57Glu	52
rs1801133		MTHFR	1	11796321	c.788C>T	p.Ala222Val	29, 53
rs2426295		NFATC2	20	51398762	c.2663–32T>A	Intronic	54
rs28362491		NFKB1	4	102500998	c.-798_-795delATTG	5’ of gene	55
rs696	rs8904	NFKBIA	14	35401887	c.*126G>A	3’ UTR	55
rs2227982		PDCD1	2	241851281	c.644C>T	p.Ala215Val	56
rs689466	rs12734919	PTGS2	1	186681619	c.-1329A>G	5’ of gene	8
rs2476601		PTPN22	1	113834946	c.1858C>T	p.Arg620Trp	57
rs7976329	rs7137890	PTPRO	12	15449705	c.76–34269T>C	Intronic	10

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SNP rs#	Proxy†	Gene	Chrm	Position††	Nucleotide Change	Protein Change	Ref
rs7574865		STAT4	2	191099907	c.274–23582A>C	Intronic	58
rs1800470		TGFB	19	41353016	c.29C>T	p.Pro10Leu	44, 59, 60
rs1800471		TGFB	19	41352971	c.74G>C	p.Arg25Pro	44, 49, 59
rs3775291		TLR3	4	186082920	c.1234C>G	p.Leu412Phe	61
rs4986790		TLR4	9	117713024	c.896A>G	p.Asp299Gly	62
rs10759932		TLR4	9	117702866	c.-1847T>C	5’ to gene	63
rs1800629		TNF	6	31575254	c.-488G>A	5’ to gene	6, 36, 44, 45, 59, 64, 65
rs1625895		TP53	17	7674797	c.672+62A>G	Intronic	66
rs17868320		UGT1A9	2	233669782	c.-2152C>T	5’ to gene	67
rs6714486		UGT1A9	2	233671659	c.-276T>A	5’ to gene	67
rs7439366		UGT2B7	4	69098620	c.802T>C	p.Tyr268His	68
rs699947		VEGFA	6	43768652	c.-2055A>C	5’ to gene	69
rs1570360	rs3025007	VEGFA	6	43770093	c.-614A>G	5’ to gene	69
rs2910164	rs2961920	MIR146A	5	160485411	n.60C>G		70
rs11614913	rs4759316	MIR196A2	12	53991815	n.78C>T		70
rs3746444	rs3746436	MIR499A	20	34990448	n.73A>G		70

† - SNP was used as a proxy when a variant was not present in the genotyping chip

†† - Assembly CRCh38.p7 used for nucleotide position

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Table 2.

Characteristics and comparisons of European American and African Americans kidney transplant recipients with and without acute rejection; % (no. of recipients)

	European Americans				African Americans			
Characteristic	**All**	**No AR**	**AR**	**P-value**	**All**	**No AR**	**AR**	**P-value**
Total	**2390**	**82.4% (1969)**	**17.6% (421)**		**482**	**85.3% (411)**	**14.7% (71)**	
Ethnicity; % (no. of recipients):								
Not Hispanic/Latino	99.4% (2318)	99.4% (1909)	99.5% (409)	0.831	99.5% (446)	99.5% (381)	100% (65)	0.5593
Hispanic/Latino	0.6% (13)	0.6% (11)	0.5% (2)		0.5% (2)	0.5% (2)		
Gender; % (no. of recipients):								
Female	37.2% (890)	38.0% (749)	33.5% (141)	0.079	37.1% (179)	36.7% (151)	39.4% (28)	0.664
Male	62.8% (1500)	62.0% (1220)	66.5% (280)		62.9% (303)	63.3% (260)	60.6% (43)	
Mean age at transplant in years; years (SD):								
	50.39 (14.7)	50.88 (14.3)	48.11 (15.9)	0.0004	46.94 (12.2)	47.17 (12.2)	45.56 (12.0)	0.301
Primary Cause of End Stage Kidney Disease; % (no. of recipients):								
Diabetes	27.2% (650)	27.3% (537)	26.8% (113)	0.024	23.7% (114)	24.6% (101)	18.3% (13)	0.218
Glomerular disease	25.2% (601)	24.4% (481)	28.5% (120)		19.1% (92)	18.0% (74)	25.4% (18)	
Hypertension	6.2% (149)	6.9% (135)	3.3% (14)		38.2% (184)	38.7% (159)	35.2% (25)	
Other	21.5% (513)	21.3% (420)	22.1% (93)		11.2% (54)	11.0% (45)	12.7% (9)	
Polycystic kidney dis.	15.8% (378)	16.3% (320)	13.8% (58)		5.2% (25)	4.6% (19)	8.5% (6)	
Unknown	4.1% (99)	3.9% (76)	5.5% (23)		2.7% (13)	3.2% (13)		
Donor Status; % (no. of recipients):								
Deceased	32.3% (773)	33.5% (659)	27.1% (114)	0.011	67.8% (327)	68.9% (283)	62.0% (44)	0.251
Living	67.7% (1617)	66.5% (1310)	72.9% (307)		32.2% (155)	82.6% (128)	38.0% (27)	
Mean donor age in years; years (SD):								
	41.99 (13.53)	41.58 (13.74)	43.89 (12.34)	0.0014	36.93 (13.93)	37.01 (14.13)	36.52 (12.86)	0.788
Donor Gender; % (no. of recipients):								
Missing	.(1)	.(1)		0.316	.(5)	.(4)	.(1)	0.072
Female	53.4% (1275)	52.9% (1041)	55.6% (234)		44.4% (212)	42.8% (174)	54.3% (38)	
Male	46.6% (1114)	47.1% (927)	44.4% (187)		55.6%6 (265)	57.2% (233)	45.7% (32)	
Cold Ischemia Time; % (no. of recipients):								

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	European Americans				African Americans			
Characteristic	**All**	**No AR**	**AR**	**P-value**	**All**	**No AR**	**AR**	**P-value**
Total	**2390**	**82.4% (1969)**	**17.6% (421)**		**482**	**85.3% (411)**	**14.7% (71)**	
Missing	.(98)	.(87)	.(11)	0.125	.(62)	.(58)	.(4)	0.185
<= 24 h	96.5% (2213)	96.3% (1812)	97.8% (401)		80.7% (339)	79.6% (281)	86.6% (58)	
>24 h	3.5% (79)	3.7% (70)	2.2%(9)		19.3% (81)	20.4% (72)	13.4% (9)	
Prior Kidney Transplant; % (no. of recipients):								
No Prior Transplants	83.9% (2006)	84.8% (1669)	80.0% (337)	0.017	89.0% (429)	89.3% (367)	87.3% (62)	0.624
Prior Transplant	16.1% (384)	15.2% (300)	20.0% (84)		11.0% (53)	10.7% (44)	12.7% (9)	
Need for dialysis in the first 14 days post-transplant; % (no. of recipients):								
No Dialysis	92.8% (2217)	93.1% (1834)	91.0% (383)	0.119	83.2% (401)	84.9% (349)	73.2% (52)	0.015
Dialysis	7.2% (173)	6.9% (135)	9.0% (38)		16.8% (81)	15.1% (62)	26.3% (19)	
Panel Reactive Antibodies; % (no. of recipients):								
Missing	.(5)	.(5)		0.244				
Zero %	46.7% (1115)	47.3% (929)	44.2% (186)		56.2% (271)	59.1% (243)	39.4% (28)	0.002
Greater than zero	53.3% (1270)	52.7% (1035)	55.8% (235)		43.8% (211)	40.9% (168)	60.6% (43)	
T or B Cell Crossmatch; % (no. of recipients):								
Missing	.(37)	.(29)	.(8)	0.0027	.(2)	.(2)		0.0013
Negative	93.8% (2207)	94.5% (1833)	90.6% (374)		94.2% (452)	95.6% (391)	85.9% (61)	
Positive	6.2% (146)	5.5% (107)	9.4% (39)		5.8% (28)	4.4% (18)	14.1% (10)	
Plasmapheresis Prior to Transplant; % (no. of recipients):								
Missing	.(129)	.(110)	.(19)	<.0001	.(10)	.(9)	.(1)	0.0013
No Plasmapheresis	97.2% (2198)	98.0% (1822)	93.5% (376)		97.2% (459)	98.3% (395)	91.4% (64)	
Plasmapheresis	2.8% (63)	2.0% (37)	6.5% (26)		2.8% (13)	1.7% (7)	8.6% (6)	
HLA mismatches; % (no. of recipients):								
Missing	.(18)	.(17)	.(1)	<.0001	.(1)	.(1)		0.582
Greater than zero	87.3% (2070)	85.7% (1673)	94.5% (397)		94.4% (454)	94.2% (386)	95.7% (68)	
Zero	12.7% (302)	14.3% (279)	5.5% (23)		5.6% (27)	5.8% (24)	4.3% (3)	
Type of Antibody Induction; % (no. of recipients):								
Combination	2.6% (63)	2.1% (42)	5.0% (21)	<.0001	2.5% (12)	2.7% (11)	1.4% (1)	0.0046
Monoclonal	36.0% (861)	37.6% (740)	28.7% (121)		42.7% (206)	45.0% (185)	29.6% (21)	
None	2.2% (52)	2.4% (47)	1.2% (5)		1.7% (8)	1.7% (7)	1.4% (1)	

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	European Americans				African Americans			
Characteristic	**All**	**No AR**	**AR**	**P-value**	**All**	**No AR**	**AR**	**P-value**
Total	**2390**	**82.4% (1969)**	**17.6% (421)**		**482**	**85.3% (411)**	**14.7% (71)**	
Polyclonal	59.3% (1416)	58.0% (1142)	65.1% (274)		53.5% (258)	51.1% (210)	67.6% (48)	
Smoking status; % (no. of recipients):								
Missing	.(90)	(80)	.(10)	0.678	.(9)	.(8)	.(1)	0.179
Current	7.9% (181)	8.1% (152)	7.1% (29)		12.3% (58)	11.2% (45)	18.6% (13)	
Past	36.4% (837)	36.5% (691)	35.5% (146)		24.7% (117)	25.5% (103)	20.0% (14)	
Never	55.7% (1282)	55.4% (1046)	57.4% (236)		63.0% (298)	63.3% (255)	61.4% (43)	
Preemptive Transplan; % (no. of recipients)t:								
Not Preemptive	62.4% (1491)	62.3% (1227)	62.7% (264)	0.880	92.1% (444)	92.5% (380)	90.1% (64)	0.504
Preemptive	37.6% (899)	37.7% (742)	37.3% (157)		7.9% (38)	7.5% (31)	9.9% (7)	
Steroid Use at Day 14 Post-Transplant; % (no. of recipients):								
On Steroids	60.6% (1448)	61.5% (1211)	56.3% (237)	0.047	58.9% (284)	58.2% (239)	63.4% (45)	0.408
Off Steroids	39.4% (942)	38.5% (758)	43.7% (184)		41.1% (198)	41.8% (172)	36.6% (26)	
Calcineurin Inhibitor Type at Transplant; % (no. of recipients):								
Both	0.1% (2)	0.1% (1)	0.2% (1)	<.0001	0.2% (1)	0.2% (1)		0.0002
Cyclosporine	23.2% (555)	21.8% (429)	29.9% (126)		11.2% (54)	8.8% (36)	25.4% (18)	
None	2.0% (47)	1.6% (31)	3.8% (16)		3.1% (15)	2.7% (11)	5.6% (4)	
Tacrolimus	74.7% (1786)	76.6% (1508)	66.0% (278)		85.5% (412)	88.3% (363)	69.0% (49)	
Simultaneous Pancreas Kidney Transplant (SPK); % (no. of recipients):								
non-SPK	93.9% (2245)	94.1% (1854)	92.9% (391)	0.316	96.5% (465)	97.1% (399)	93.0% (66)	0.082
SPK	6.1% (145)	5.9% (115)	7.1% (30)		3.5% (17)	2.9% (12)	7.0% (5)	
Prior Non-kidney Transplants; % (no. of recipients):								
No Prior Transplants	87.5% (2091)	88.1% (1735)	84.6% (356)	0.045	96.1% (463)	96.6% (397)	93.0% (66)	0.146
Prior Transplant	12.5% (299)	11.9% (234)	15.4% (65)		3.9% (19)	3.4% (14)	7.0% (5)	
Cytomegalovirus Recipient/Donor Status; % (no. of recipients):								
Missing	.(76)	.(67)	.(9)	0.199	.(12)	.(8)	.(4)	0.950
Recipient(-)/Donor(-)	28.0% (647)	27.5% (523)	30.1%(124)		8.1% (38)	7.9% (32)	9.0% (6)	
Recipient (+)	51.8% (1199)	52.7% (1002)	47.8% (197)		78.9% (371)	79.2% (319)	77.6% (52)	
Recipient(-)/Donor(+)	20.2% (468)	19.8% (377)	22.1% (91)		13.0% (61)	12.9% (52)	13.4% (9)	

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Table 3.

Frequencies of tested alleles and P-values of SNPs for 12 month and all time acute rejection for both European-American and African-American cohorts adjusted for clinical factors.

		European-American Recipients			African-American Recipients		
SNP rs#	**Gene**	**TAF**	**12 month P-value**	**All Time P-value**	**TAF**	**12 month P-value**	**All Time P-value**
rs4148738	ABCB1	0.558	0.65	0.98	0.756	0.19	0.051
rs2269475	AIF	0.146	0.67	0.89	0.103	0.63	0.65
rs5186	AT1R	0.301	0.14	0.15	0.054	0.25	0.41
rs55637918	DEUP1 (CCDC67)	0.100	0.12	0.51	0.303	0.36	0.075
rs1024611	CCL2	0.272	0.35	0.23	0.188	0.97	0.51
rs2107538	CCL5	0.166	0.49	0.44	0.429	0.21	0.20
rs1799864	CCR2	0.098	0.18	0.31	0.173	0.74	0.94
rs1799987	CCR5	0.444	0.42	0.53	0.585	0.77	0.89
rs10490574	CD28	0.184	0.048	0.051	0.056	0.55	0.32
rs1129055	CD86	0.274	0.62	0.56	0.172	0.084	0.096
rs733618	CTLA4	0.081	0.17	0.26	0.141	0.53	0.14
rs5742909	CTLA4	0.095	0.0049	0.012	0.016	0.94	0.58
rs231775	CTLA4	0.391	0.034	0.018	0.399	0.27	0.13
rs3087243	CTLA4	0.427	0.96	0.85	0.200	0.53	0.63
rs4073	CXCL8	0.525	0.23	0.15	0.224	0.69	0.99
rs2515641	CYP2E1	0.892	0.66	0.80	0.395	0.82	0.68
rs776746	CYP3A5	0.068	0.21	0.050	0.694	0.67	0.56
rs4149257	EPHX2	0.254	0.54	0.41	0.787	0.44	0.19
rs1799963	F2	0.017	0.45	0.74	0.004	0.99	0.99
rs6025	F5	0.970	0.077	0.083	0.997	0.082	0.37
rs7851696	FCN2	0.114	0.23	0.37	0.220	0.19	0.55
rs1801274	FCGR2A	0.507	0.26	0.12	0.554	0.37	0.030
rs9296068	HLA-DOA	0.331	0.18	0.094	0.539	0.94	0.22
rs1063320	HLA-G	0.490	0.015	0.050	0.602	0.053	0.47
rs5498	ICAM1	0.422	0.90	0.84	0.189	0.92	0.44
rs1143634	IL1B	0.236	0.29	0.11	0.140	0.60	0.099
rs2069762	IL2	0.301	0.76	0.90	0.093	0.68	0.90

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		European-American Recipients			African-American Recipients		
SNP rs#	Gene	TAF	12 month P-value	All Time P-value	TAF	12 month P-value	All Time P-value
rs228942	IL2RB	0.176	0.25	0.42	0.095	0.22	0.19
rs2284033	IL2RB	0.425	0.65	0.94	0.430	0.76	0.44
rs657075	IL3	0.102	0.41	0.41	0.026	0.36	0.27
rs61527852	IL3	0.090	0.25	0.18	0.126	0.066	0.027
rs31480	IL3	0.221	0.71	0.82	0.145	0.77	0.36
rs2243250	IL4	0.143	0.98	0.78	0.657	0.92	0.84
rs1801275	IL4R	0.214	0.24	0.51	0.678	0.58	0.90
rs1524107	IL6	0.050	0.048	0.20	0.085	0.45	0.37
rs1800795	IL6	0.574	0.15	0.26	0.925	0.67	0.96
rs1800896	IL10	0.490	0.75	0.64	0.356	0.19	0.090
rs1800871	IL10	0.764	0.75	0.83	0.610	0.91	0.85
rs1800872	IL10	0.764	0.75	0.83	0.610	0.91	0.85
rs763780	IL17F	0.048	0.21	0.38	0.074	0.59	0.81
rs187238	IL18	0.270	0.11	0.094	0.215	0.67	0.83
rs2278293	IMPDH1	0.454	0.63	0.86	0.481	0.66	0.98
rs2278294	IMPDH1	0.350	0.88	0.67	0.425	0.84	0.52
rs11706052	IMPDH2	0.104	0.72	0.74	0.014	0.72	0.22
rs2430561	INFG	0.238	0.50	0.59	0.167	0.95	0.76
rs3807307	IRF5	0.476	0.68	0.95	0.293	0.041	0.052
rs5918	ITGB3	0.149	0.59	0.46	0.108	0.078	0.15
rs7096206	MBL2	0.779	0.20	0.51	0.844	0.66	0.58
rs5030737	MBL2	0.073	0.92	0.77	0.006	0.23	0.41
rs1800450	MBL2	0.134	0.67	0.75	0.034	0.75	0.50
rs1800451	MBL2	0.015	0.89	0.84	0.231	0.28	0.45
rs1801133	MTHFR	0.329	0.94	0.76	0.107	0.84	0.45
rs2426295	NFATC2	0.073	0.22	0.82	0.063	0.36	0.38
rs28362491	NFKB1	0.383	0.29	0.71	0.513	0.22	0.34
rs8904	NFKBIA	0.380	0.87	0.42	0.594	0.93	0.75
rs2227982	PDCD1	0.009	0.24	0.52	0.01	0.99	0.69
rs12734919	PTGS2	0.178	1.00	0.68	0.035	0.49	0.31

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		European-American Recipients			African-American Recipients		
SNP rs#	**Gene**	**TAF**	**12 month P-value**	**All Time P-value**	**TAF**	**12 month P-value**	**All Time P-value**
rs2476601	PTPN22	0.880	0.95	0.84	0.985	0.52	0.77
rs7137890	PTPRO	0.343	0.18	0.34	0.174	0.79	0.92
rs7574865	STAT4	0.773	0.90	0.84	0.845	0.94	0.68
rs1800470	TGFB	0.620	0.37	0.93	0.546	0.87	0.69
rs1800471	TGFB	0.077	0.47	0.42	0.067	0.89	0.96
rs3775291	TLR3	0.292	0.70	0.76	0.074	0.35	0.27
rs4986790	TLR4	0.052	0.30	0.19	0.070	0.95	0.78
rs10759932	TLR4	0.139	0.30	0.78	0.238	0.0089	0.0046
rs1800629	TNF	0.195	0.75	0.90	0.110	0.86	0.55
rs1625895	TP53	0.882	0.97	0.98	0.726	0.72	0.49
rs17868320	UGT1A9	0.060	0.46	0.50	0.025	0.79	0.54
rs6714486	UGT1A9	0.061	0.41	0.44	0.197	0.96	0.36
rs7439366	UGT2B7	0.462	0.48	0.19	0.706	0.068	0.17
rs699947	VEGFA	0.507	0.23	0.25	0.791	0.29	0.32
rs3025007	VEGFA	0.456	0.83	0.82	0.334	0.61	0.62
rs2961920	MIR146A	0.768	0.59	0.45	0.576	0.0019	0.00011
rs4759316	MIR196A2	0.558	0.84	0.68	0.604	0.96	0.95
rs3746436	MIR499A	0.189	0.48	0.69	0.165	0.43	0.38

TAF – Tested allele frequency