Genome-Wide Association Meta-Analysis for Acute Rejection of Kidney Transplants

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INTRODUCTION

Evidence is limited regarding acute rejection (AR) beyond human leukocyte antigens and studies investigating genetic background of AR are limited in size. This study combined genome-wide association studies (GWAS) following kidney transplantation to increase power and further understand mechanisms of AR. GWAS has led to the elucidation of thousands of genetic associations across many polygenic traits and diseases with heritable components. The cohorts in this meta-analysis are from the International Genetics and Translational Research in Transplantation Network (iGeneTRAiN).

METHODS

We performed a GWAS meta-analysis of AR anytime post-transplant in Caucasian recipients and donors after kidney transplantation using the "Tx Array" containing approximately 782,000 single-nucleotide polymorphisms (SNPs). AR was defined by treating physician. Genotype imputation was carried out based on the 1000 Genomes project and Genomes of The Netherlands reference datasets.

The analysis was adjusted for age, sex, living versus deceased donors, and population stratification using principal components. We ran a fixed effect, inverse variance, meta-analysis to combine results from 7 cohorts. SNPs that were deemed to reach GWAS significance had $p < 1x10^{-6}$, population frequency between 0.01 and 0.99 and R^2 for imputation quality > 0.8.

7 GWAS Cohorts in Meta-Analysis: Deterioration of Kidney Allograft Function (DeKAF Genomics) (USA and Canada), Dublin (Ireland), TransplantLines (Netherlands), Leiden (Netherlands), Scripps (USA), Vanderbilt (USA), Vienna (Austria)

RESULTS

7 GWAS cohorts with Caucasian kidney transplant recipients were included in the study are described in Tables 1 and 2.

Table 1: AR and Donor Type in iGeneTRAiN Meta-Analysis

		Living Donors		AR Events	
Study Name	N	N	%	N	%
TransplantLines	1106	255	23	369	33
Dublin	315	0	0	130	41
DeKAF	1939	1282	66	325	17
Leiden	277	115	42	45	16
Scripps	378	289	76	59	16
Vanderbilt	659	179	27	77	12
Vienna	617	90	15	260	42
Total	5291	2210	42	1265	24

RESULTS

Table 2: Characteristics of Subjects in iGeneTRAiN GWAS Meta-Analysis

	Study Name													
	DeKAF Genomics		Dublin		TransplantLines		Leiden		Scripps		Vanderbilt		Vienna	
Characteristic	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Ethnicity:														
White/Caucasian	1939	100	315	100	837	76	277	100	378	100	659	100	617	100
Not Obtained	0	0	0	0	269	24								
Male	1223	63.07	210	67	634	57	188	68	230	61	400	61	392	63.5
Mean age at enrollment in years	50.39				48		52		48		45		51	
Cause of End Stage Kidney Disease:														
Diabetes	553	28.53	N/A	N/A	41	4	22	7.9					81	13.1
Glomerular disease	446	23.01	128	41	294	27	14	5.1					210	34
Hypertension	132	6.81	25	8	90	8							62	10
Polycystic kidney disease	308	15.89	52	17	155	14	52	19					93	15.1
Other	432	22.29	82	26	526	48							171	27.7
Not recorded/unknown	67	3.46	28	9										
Living donor transplant	1282	66.15	0	0	255	23	115	42	289	76	179	27	90	14.6
Mean donor age in years	42		0	0	44		48						50	
Male donor	904	46.67	192	61	562	51	134	48					350	56.7
AR in first 3 months post-transplant	167	8.61	102	32	332	30	25	56					166	26.9

Figure 1: Manhattan Plot for Recipient SNPs

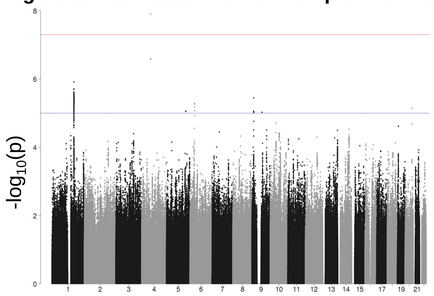
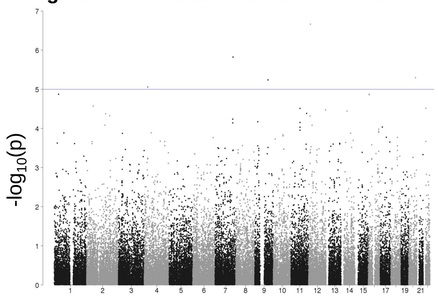


Figure 2: Manhattan Plot for Donor SNPs



RESULTS

Recipient SNPs

30 recipient SNPs reached GWAS significance for their association with AR.

The recipient SNP with strongest AR association was rs294768 ($p = 1.24 \times 10^{-8}$) located 7.9 kb 5' of *UGT2B10*. 14 of the 30 top recipient SNPs were located in or near *UGT2B10,* including rs2942857, which is an mRNA splice acceptor ($p = 2.59 \times 10^{-7}$).

3 significant recipient SNPs were located in or near each of *UNC5D*, *CA10*, and *NLGN1*

Donor SNPs

39 donor SNPs reached GWAS significance for their association with AR.

The top donor SNPs were: rs137878631, 33kb 3' of *DMP1* ($p = 2.61 \times 10^{-8}$); rs78140122, intron of *MARCH1* ($p = 4.16 \times 10^{-8}$); rs140005264, intron of *ALDH16A1*($p = 7.34 \times 10^{-8}$); and rs62220573,19kb 3' of *KRTAP21-3* ($p = 9.52 \times 10^{-8}$).

The remaining significant donor SNPs were located in or near the following genes: *EVX2*, *ATF7IP*, *MIR2054*, *TAS2R16*, *GPATCH1*, *RAB3GAP2*, *KIAA1328*, *FAM107B*, *ALDH16A1*, *TPP2*, *TXNDC5*, *ADAMTS19*, *HERPUD2* and 7 SNPs 3' of *FGFR2*,

CONCLUSIONS AND FUTURE DIRECTIONS

We identified several novel susceptibility loci associated with AR. *UGT2B10* had the most variants associated with AR in this meta-analysis with $p < 1x10^{-6}$. These SNPs need to be validated by independent cohorts and functionally assessed.

Future GWAS meta-analyses will be sub-stratified by AR subtypes such as acute cellular rejection, antibody mediated rejection, and biopsy proven rejection to account for the different classifications and the different phenotype ascertainment. We will also conduct GWAS time to AR event analyses within the first 12 months using standard methodologies.

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To join iGeneTRAiN contact Ajay Israni: isran001@umn.edu or visit igenetrain.org