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REVIEW

Genetics of acute rejection after kidney transplantation

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SUMMARY

Treatment of acute rejection (AR) following kidney transplantation has improved in recent years, but there are still limitations to successful outcomes. This review article covers literature in regard to recipient and donor genetics of AR kidney and secondarily of liver allografts. Many candidate gene and some genome-wide association studies (GWASs) have been conducted for AR in kidney transplantation. Genetic associations with AR in kidney and liver are mostly weak, and in most cases, the associations have not been reproducible. A limitation in the study of AR is the lack of sufficiently large populations that account for population stratification to study the AR phenotype which in this era occurs in <10% of transplants. Furthermore, the AR phenotype has been difficult to define and the definitions of classifications have evolved over time. Literature related to the pharmacogenomics of tacrolimus is robust and has been validated in many studies. Associations between gene expression and AR are emerging as markers of outcomes and AR classification. In the future, combinations of pretransplant genotype for AR risk prediction, genotype-based immune suppressant dosing, and pharmacogenomic markers to select AR maintenance or treatment and expression markers from biopsies may provide valuable clinical tools for guiding treatment.

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Introduction

This article is a review of literature pertaining to the genetics of acute rejection (AR) in kidney, and to some extent liver, allograft recipients. There are three primary types of allograft rejection: hyperacute rejection that occurs minutes after the transplant, AR, which occurs days to months after transplant, and chronic rejection that occurs long after transplant. AR has further been classified as antibody-mediated rejection (ABMR), T cell-mediated rejection (TCMR), C4d-negative ABMR, and mixed; in this review, we focused on all forms of AR. The definition of the AR phenotype has changed over time as it is further understood. Mechanistically, these types of AR are quite different but have a similar endpoint of the allograft being rejected. Thus, the heterogeneity of the AR phenotype has made genetic association studies difficult to determine and validate. As there is continual updating of the classification and definition of AR, such as the Banff classifications [1,2], this review article does not restrict manuscripts reviewed to a single

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AR definition, but leaves the definition to the authors of the reviewed literature.

As with the definition of AR, methods used to study the genetics associated with AR have also changed over time. DNA and/or RNA is extracted from the blood or the biopsy and then genetically assessed for association with AR. These association tests have evolved from testing candidate single nucleotide polymorphisms (SNPs), to testing multiple candidate SNPs, then panels of SNPs on gene chips, to genome-wide SNP chips, and we are now identifying known and novel SNPs using whole-genome and targeted next-generation sequencing. The majority of these AR studies were case controls investigating recipients with or without AR. Although some of these studies account for population stratification, such as a recent GWAS [3], many of them did not. This article also reviews literature on the pharmacogenomics and transcriptomics of AR.

Single nucleotide polymorphisms associated with acute rejection

Although outcome after solid organ transplants has improved in recent years, success is still limited by AR, chronic rejection (chronic allograft nephropathy), and graft failure. AR has been repeatedly shown to be one of the strongest predictors of allograft survival, and therefore, there is great interest in finding genetic markers associated with AR and AR risk [4]. Throughout the last few decades, there have been multiple reports in which investigators have attempted to associate genetic variation with AR risk. The strongest association between genetic variants and transplant outcome has been with the major histocompatibility complex (MHC) antigens, also called human leukocyte antigens (HLA) [5]. Because of this strong association, transplant centers try to match as many HLA alleles between the donor and the recipient to lower the immunogenicity of the allograft and reduce the risk of AR. There have also been additional reports showing an association with AR of genetic variants in other genes. Most genetic association studies aim to find interesting genes and then attempt to understand the biological relevance for those genes to AR. It is difficult to use the genetic association studies to predict susceptibility for AR because of small effect size of individual SNPs and the heterogeneous nature of AR. These genes would include those in immune pathways, both innate and adaptive immune systems, stimulatory molecules, tissue repair pathways, and genes involved in systemic hypertension among others.

For many variants, the initial report for a given SNP presents with a statistically significant association with AR; however, validation for most of these SNPs has remained elusive [6–9]. We identified 76 variants in the literature which were associated with AR (Table 1). This list was compiled from an extensive literature search of numerous genetic variants that have been associated with AR in kidney and some liver transplant studies. Nearly all the reports in Table 1 are from candidate gene analysis of recipient genomic DNA. Few studies have been conducted that investigate the genetic interactions between donor and recipient beyond HLA matching. Given the small cohort size of most transplant studies, donor and recipient genetics have not been thoroughly studied in combination. Note that there are several limitations of the reports in the literature. As stated in the Introduction, there are variations in the definition of AR between studies and that definition has changed over time. Additionally, population stratification was not done in the analysis for many of the reviewed studies. In most of these reports, the statistical power to detect a true association was low. It is common for small cohorts to be used in the analysis ($N < 300$) or to not take into account the testing of multiple SNPs. Additionally, validation cohorts are typically absent in the studies, or subsequent studies failed to validate the initial positive reports. Validation could fail because of the heterogeneity of the AR phenotype. Each type of AR has different mechanisms, so each type would likely have different genetics and thus be difficult to validate unless large sample sizes of each type of AR are obtained. However, some of these SNPs in Table 1 have been associated with AR by multiple studies, such as *ACE* (rs4340), *CCR2* (rs1799864), *CCR5* (rs1799987), *CD28C* (rs3116496), *CTLA4* (rs5742909, rs231775), *F5* (rs6025) and *IL10* (rs1800896, rs1800872). Most of these studies have focused on recipient SNPs, but there have been a few studies analyzing donor-related SNPs. At present, there are no candidate SNPs that have been unambiguously shown to be associated with AR, through the use of large (1000+) discovery and validation cohorts.

The choice of candidate SNPs for investigation is typically limited to those that have come to the attention of the investigator, either through previous reports, or were hypothesized to be important variants which functionally impact a protein in a biological pathway thought to impact the occurrence of AR. A GWAS allows for multiple variants spanning the entire genome to be investigated. Therefore, the GWAS provides a more robust platform for discovery than single SNP

Table 1. Genetic variants associated with acute rejection.

Gene	Name	SNP rs#	Protein change	Nucleotide change	Organ	Study *n*, #AR, # test	*P*-value, OR (95% CI) [ref]
ABCB1	ATP-binding cassette, subfamily B, member 1	rs2032582	p.Ser893Alap. Ser893Thr	c.2677T>Ac. 2677T>G	K	*N* = 232, 64, 21	*P* = 0.003, 3.16 (1.50–6.67) [92]
ACE	Angiotensin I-converting enzyme	rs4340	Intronic	288 bp in/del	K K	*N* = 206, 19, 4 *N* = Meta-analysis	*P* < 0.05, 5.34 (1.27–22.42) [93]1. 62 (1.14–2.29) [94]
AIF	Allograft inflammatory factor-1	rs2269475	p.Arg15Trp	c.43C>T	K	*N* = 458, 118, 3	*P* = 0.05, 0.61 (0.39–0.97) [95]
AT1R	Angiotensin type 1 receptor	rs5186	3′ UTR	c.*86A>C	K	*N* = 206, 19, 4	*P* < 0.05, 8.34 (2.43–28.69) [93]
CCDC67	Coiled-coil domain containing 67	rs10765602	5′ of gene	g.93048165G>T	K	*N* = 778, 503, GWAS	*P* = 0.02 1.98 (1.21–3.25) [12]
CCL2	C-C motif chemokine ligand 2	rs1024611	5′ of gene	c.-2582A>G	K	*N* = 167, 27, 2	*P* = 0.022, 2.6 (1.12–6.01) [96]
CCL5	C-C motif chemokine ligand 5	rs2107538	5′ of gene	c.-471G>A	K	*N* = 261, 92, 3	*P* = 0.035, None, [97]
CCR2	C-C motif chemokine receptor 2	rs1799864	p.Val64Ile	c.190G>A	K K	*N* = 163, 39, 5 *N* = 85, 33, 2	*P* = 0.014, 0.30 (0.12–0.78) [98]*P* = 0.003, None [99]
CCR5	C-C motif chemokine receptor 5	rs1799987	Intronic	c.-301+246A>G	K K K	*N* = 163, 39, 5 *N* = 243, 46‡, 2 *N* = 85, 33, 2	*P* = 0.016, 0.37 (0.16–0.85) [98]*P* = 0.029, 2.76 (1.11–6.90) [100]*P* = 0.003, None [99]
CD28	CD28 molecule	rs3116496	Intronic	c.243+17T>C	K K	*N* = 270, 70, 1	*P* = 0.026, 1.93 (1.10–3.39) [101]meta-analysis [102]
CD46	CD46 molecule	rs2796267	5′ of gene	c.-652G>A	K	*N* = 334, 68, 1	*P* = 0.012, 0.47 (0.26–0.84) [103]
CD86	CD86 molecule	rs1129055	p.Ala198Thr	c.592G>A	K, L	*N* = Meta-analysis	Meta-analysis [102]
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	rs733618	5′ of gene	c.-1722T>C	K	*N* = 167, 45, 5	*P* = 0.002, 0.411 (0.24–0.72) [104]
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	rs5742909	5′ of gene	c.-319C>T	K K	*N* = 131, 34, 5 *N* = Meta-analysis	*P* = 0.015, 3.45 (1.18–10.1) [105]*P* = 0.014, 0.805 (0.68–0.96) [106]
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	rs231775	p.Thr17Ala	c.49A>G	K K K K	*N* = 190, 36, 7 *N* = 63, 17, 12 *N* = Meta-analysis *N* = 72, 29, 5	*P* = 0.0374, 2.78 (1.07–7.19) [107]*P* = 0.043, 5.5 (0.962–31.44) [108]Meta-analysis [109]*P* = 0.028, 0.30 [104]
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	rs3087243	3′ of gene	c.*1421G>A	K	*N* = 72, 29, 5	*P* = 0.035, 4.51 [110]
CXCL8	C-X-C motif chemokine ligand 8	rs4073	5′ of gene	c.-352A>T	K	*N* = 296, 61, 2	*P* = 0.032, 2.7 (1.09–6.69) [111]

Table 1. Continued.

Gene	Name	SNP rs#	Protein change	Nucleotide change	Organ	Study *n*, #AR, # test	*P*-value, OR (95% CI) [ref]
CYP2E1	Cytochrome P450 2E1	rs2515641	p.Phe421=p. Phe421Leu	c.1263C>Gc. 1263C>T	K	*N* = 347, 63, 3	*P* = 0.003, 2.55 (1.37–4.75) [112]
CYP3A5	Cytochrome P450 3A5	rs776746	Intronic	c.219-237G/A	K	*N* = 136, 19, 3	*P* = 0.01, 10.1 (1.21–83.3) [113]
EPHX2	Epoxy hydrolase 2	rs1042032	3′ UTR	c.*35A>G	K	*N* = 259, 31, 3	*P* = 0.015, 6.34 (1.35–29.90) [114]
F2	Coagulation factor II, thrombin	1799963	3′ UTR	c.*97G>A	K	*N* = 165, 39, 3	*P* = 0.03, 12.2 (1.3–118.7) [115]
F5	Coagulation factor V	rs6025	p.Arg534Gln	c.1601G>A	K	*N* = 394, 192, 1	*P* < 0.02, 3.83 (1.38–10.59)
						N = 165, 39, 3	[116]*P* = 0.01, 5.7 (1.6–20.2) [115]
FOXP3	Forkhead box P3	rs2232365	5′ UTR	c.-22-902A>G	K	*N* = 292, 56, 6	*P* = 0.001, 3.10 (1.58–6.08) [117]
FOXP3	Forkhead box P3	rs3761548	5′ UTR	c.-23+2882A>C	K	*N* = 292, 56, 6	*P* < 0.001, 3.08 (1.67–5.660 [117]
FCGR2A	Fc fragment of IgG receptor IIA	rs1801274	p.His166Arg	c.500A>G	K	*N* = 99, 53, 1	*P* < 0.05, None [118]
HLA-DOA	Major histocompatibility complex, class II, DO alpha	rs9296068	5′ of gene	g.4470122T>G	L	*N* = 122, 60, 2	*P* = 0.001, 2.55 (1.44–4.61) [119]
HLA-DOA	Major histocompatibility complex, class II, DO alpha	rs2395304	5′ of gene	g.4464339C>T	L	*N* = 122, 60, 2	*P* = 0.008, 2.34 (1.20–4.65) [119]
HLAG	Major histocompatibility complex, class I, G	rs66554220		14 bp in/del	L	*N* = 146, 57, 2	*P* =< 0.001, 17.657 (3.73–83.67) [120]
HLAG	Major histocompatibility complex, class I, G	rs1063320	3′ UTR	c.*233C>G	L	*N* = 146, 57, 2	*P* =< 0.001, 6.80 (2.58–17.91) [120]
ICAM1	Intercellular adhesion molecule-1	rs5498	p.Lys469Glu	c.1405A>G	K	*N* = 42, 11, 2	*P* = 0.013, 0.23 (None) [121]
IL1B	Interleukin 1 beta	rs1143634	p.Phe105=	c.315C>T	K	*N* = 100, 18, 12	*P* = 0.045, 3.11 (1.02–9.44) [122]
IL2	Interleukin 2	rs2069762	5′ of gene	c.-385T>G	K	*N* = 63, 20, 1	*P* < 0.05, None, [123]
IL2RB	Interleukin 2 receptor subunit beta	rs228942	p.Asp391Glu	c.1173C>A	K	*N* = 337, 61, 4	*P* = 0.0096 2.11 (1.19–3.74) [124]
IL2RB	Interleukin 2 receptor subunit beta	rs228953	p.Gly250=	c.750C>T	K	*N* = 337, 61, 4	*P* = 0.029 1.58 (1.04–2.38) [124]
IL3	Interleukin 3	rs181781	5′ of gene	c.-1285G>A	K	*N* = 330, 60, 3	*P* = 0.041 0.55 (0.31–0.98) [125]
IL3	Interleukin 3	rs2073506	5′ of gene	c.-1662C>A	K	*N* = 330, 60, 3	*P* = 0.003 0.32 (0.15–0.68) [125]
IL3	Interleukin 3	rs40401	p.Pro27Ser	c.79C>T	K	*N* = 330, 60, 3	*P* = 0.014 2.18 (1.17–4.05) [125]
IL4	Interleukin 4	rs2243250	5′ of gene	c.-589C>T	K	*N* = 120, 14, 4	*P* = 0.02, **donor** None, [126]
IL4R	Interleukin 4 receptor	rs1801275	p.Gln576Arg	c.1727A>G	K	*N* = 344, 62, 5	*P* = 0.019, 0.44 (0.21–0.91) [127]
IL6	Interleukin 6	rs1800796	5′ of gene	c.-636G>C	L	*N* = 335, 40, 1	*P* = 0.033, 0.45 (0.21–0.98) [128]
IL6	Interleukin 6	rs1800795	5′ of gene	c.-237C>G	K	*N* = 145, 77, 20	*P* = 0.0002 **donor** [129]
IL10	Interleukin 10	rs1800896	5′ of gene	c.-1117A>G	K	*N* = 291, 50, 8	*P* = 0.016*, 1.9 (1.1–3.1)
					K	*N* = 95, 21‡, 2	[130]*P* = 0.045, 2.8 (1.17–6.69) [131]
IL10	Interleukin 10	rs1800871	5′ of gene	c.-854T>C	K	*N* = 291, 50, 8	*P* = 0.016*, 1.9 (1.1–3.1) [130]

Table 1. Continued.

Gene	Name	SNP rs#	Protein change	Nucleotide change	Organ	Study *n*, #AR, # test	*P*-value, OR (95% CI) [ref]
IL10	Interleukin 10	rs1800872	5′ of gene	c.-627A>C	K K	*N* = 232, 64, 21 *N* = 291, 50, 8	*P* = 0.007, 4.71 (1.52–14.55) [92]*P* = 0.016*, 1.9 (1.1–3.1) [130]
IL18	Interleukin 18	rs187238	5′ of gene	c.-368G>C	K	*N* = 226, 37, 1	*P* = 0.015, 3.65 (1.24–10.79) [132]
IMPDH1	Inosine 5-prime-monophosphate dehydrogenase 1	rs2278293	Intronic	c.579+119G>A	K	*N* = 191, 29, 11	*P* = 0.008, 0.34 (0.15–0.76) [133]
IMPDH1	Inosine 5-prime-monophosphate dehydrogenase 1	rs2278294	Intronic	c.580-106G>A	K	*N* = 191, 29, 11	*P* = 0.02, 0.40 (0.18–0.89) [133]
IMPDH2	Inosine 5-prime-monophosphate dehydrogenase 2	rs11706052	Intronic	c.819+10T>C	K	*N* = 232, 64, 21	*P* = 0.006, 3.39 (1.42–8.09) [92]
INFG	Interferon-γ	rs2430561	Intronic	c.115-483A>T	K	*N* = 118, 20, 4	*P*-None, 2.6 (1.6–6.0) [134]
IRF5	Interferon regulatory factor 5	rs3757385	5′ of gene	c.-811T>G	L	*N* = 289, 39, 3	*P* = 0.042, 2.34 (1.07–5.10) [135]
ITGB3	Integrin subunit beta 3	rs5918	p.Leu59Pro	c.176T>C	K	*N* = 119, 52, 1	*P* = 0.04, 2.75 (1.01–7.93) [136]
MBL2	Mannose-binding lectin	Haplotypers 7096206rs 5030737rs 1800450rs 1800451	5′ of genep. Arg52Cyp. Gly54Aspp. Gly57Glu	c.-290C>Gc. 154C>Tc. 161G>Ac. 170G>A	K	*N* = 710, 144, 11	*P* = 0.01 2.05 (1.16–3.64) [137]
MTHFR	Methylenetetrahydrofolate	rs1801133	p.Ala222Val	c.788C>T	K K	*N* = 165, 39, 3 *N* = 585, 98, 19	P = 0.04, 4.3 (1.4–12.9) [8,115]
NFKB1	Nuclear factor kappa B subunit 1	rs28362491	5′ of gene	c.-798_-795delATTG	K	*N* = 292, 56, 6	*P* = 0.001, 2.61 (1.50–4.53) [117]
NFKBIA	NFKB inhibitor alpha	rs696	3′ UTR	c.*126G>A	K	*N* = 292, 56, 6	*P* = 0.007, 1.85 (1.18–2.91) [117]
PDCD1	Programmed cell death 1	rs2227982	p.Ala215Val	c.644C>T	K	*N* = 122, 60, 4	*P* = 0.04, 0.30 (0.09–1.02) [138]
PTGS2	Prostaglandin-endoperoxide synthase 2	rs689466	5′ of gene	c.-1329A>G	K	*N* = 458, 118, 3	*P* = 0.01 0.59 (0.38–0.91) [95]
PTPN22	Protein tyrosine phosphatase nonreceptor 22	rs2476601	p.Arg620Trp	c.1858C>T	L	*N* = 345, 180, 6	*P* = 0.022, 2.33 (1.13–4.79) [139]

Table 1. Continued.

Gene	Name	SNP rs#	Protein change	Nucleotide change	Organ	Study *n*, #AR, # test	*P*-value, OR (95% CI) [ref]
PTPRO	Protein tyrosine phosphatase receptor-type O	rs7976329	Intronic	c.76-34269T>C	K	*N* = 778, 503, GWAS	*P* = 0.01, 1.61 (0.96–2.70) [12]
STAT4	Signal transducer and activator of transcription 4	rs7574865	Intronic	c.274-23582A>C	K	*N* = 453, 134, 1	*P* = 0.003, 0.542 (0.36–0.82 [140]
TGFB	Transforming growth factor-β1	rs1800470	p.Pro10Leu	c.29C>T	K K K	*N* = 291, 50, 8 *N* = 164, 7 *N* = 359, 165, 6	*P* = 0.043‡, 1.8 (1.0–3.0) [130]*P* = 0.02, 4.0 (None) [141]*P* = 0.000, 0.146 (0.076–0.281 [142]
TGFB	Transforming growth factor-β1	rs1800471	p.Arg25Pro	c.74G>C	K K K	*N* = 291, 50, 8 *N* = 118, 20, 4 *N* = 164, 13‡, 7	*P* = 0.043†, 1.8 (1.0–3.0) [130]*P* = None, 0.09 (0.02–0.49) [134]*P* = 0.02, 4.0 (None) [141]
TGFBR2	Transforming growth factor-β receptor II	rs2228048	p.Asn414=	c.1242C>T	K	*N* = 347, 63, 3	*P* = 0.020 [143]
TLR3	Toll-like receptor 3	rs3775291	p.Leu412Phe	c.1234C>G	L	*N* = 100, 37, 10	*P* = 0.017, 0.1 (0.01–0.86) [144]
TLR4	Toll-like receptor 4	rs4986790	p.Asp299Gly	c.896A>G		*N* = 238, 57, 2	*P* = 0.01, 0.41 (0.30–0.83) [145]
TLR4	Toll-like receptor 4	rs10759932	5′ of gene	c.-1847T>C		*N* = 216, 42, 6	*P* = 0.001, 0.25 (0.11–0.57) [146]
TNF	Tumor necrosis factor	rs1800629	5′ of gene	c.-488G>A	K K K K K 	*N* = 232, 64, 21 *N* = 100, 18, 12 *N* = 291, 50, 8 *N* = 95, 21, 2 *N* = 164, 13‡, 7 *N* = 129, 57, 2 *N* = 623, 1	*P* = 0.029, 2.18 (1.08–4.41) [92]*P* = 0.03, 6.277 (1.18–33.2) [122]*P* = 0.003, 5.0 (3.0–8.3) [130]*P* = 0.005, 3.92 (1.61–9.57) [131]*P* = 0.009, 6.1 (None) [141]*P* < 0.05, 2.53 (1.19–5.37) [147]*P* = 0.001, 4.05 (1.76–9.28) [148]
TP53	Tumor protein gene	rs1625895	Intronic	c.672+62A>G	K	*N* = 100, 31, 1	*P* = 0.009, 0.36 (0.16–0.78) [149]
UGT1A9	Uridine diphosphate glucuronosyltransferase 1A9	rs17868320	5′ of gene	c.-2152C>T	K	*N* = 100, 18, 3	*P* = 0.07, 3.62 (0.90–14.5) [150]
UGT1A9	Uridine diphosphate glucuronosyltransferase 1A9	rs6714486	5′ of gene	c.-275T>A	K	*N* = 100, 18, 3	*P* = 0.05, 4.40 (1.05–18.4) [150]
UGT2B7	Uridine diphosphate glucuronosyltransferase 2B7	rs7439366	p.Tyr268His	c.802T>C	K	*N* = 235, 38, 1	*P* < 0.046, 2.5 (1.00–6.41) [151]
VEGFA	Vascular endothelial growth factor A	rs699947	5′ of gene	c.-2055A>C	K	*N* = 173, 65, 4	*P* = 0.005, 4.1 (1.5–11.3) [152]

Table 1. Continued.

Gene	Name	SNP rs#	Protein change	Nucleotide change	Organ	Study *n*, #AR, # test	*P*-value, OR (95% CI) [ref]
VEGFA	Vascular endothelial growth factor A	rs1570360	5′ of gene	c.-614A>G	K	*N* = 173, 65, 4	*P* = 0.001, 6.8 (1.8–25.0) [152]
MIR146A	MicroRNA 146a	rs2910164		n.60C>G	K	*N* = 350	*P* = 0.04, 2.63 (1.04–6.62) [153]
MIR196A2	MicroRNA 196a-2	rs11614913		n.78C>T	K	*N* = 350	*P* = 0.027, 2.86 (1.12–7.27) [153]
MIR499A	MicroRNA 499a	rs3746444		n.73A>G	K	*N* = 350	*P* = 0.027, 3.31 (1.14–9.58) [153]

L, liver transplant; K, kidney transplant.
All SNPs in the table are in recipients, unless otherwise noted.
"Study *n*" is the number of individuals used in that candidate gene study to determine the *P*-value.
"# test" is the number of polymorphisms tested in the reported analysis.
AR is the number of acute rejection events in the study population.
*Significant *P*-value based on an IL-10 haplotype containing three promoter variants.
†Significant *P*-value based on haplotype containing the codon 10 and codon 25 TGFB variants.
‡0 and 1 acute rejection events were combined in the no rejection category for analysis.

analysis. A limitation to GWAS analysis is the high expectation of statistical significance (typically a *P*-value threshold of 10^{-8}) due to multiple testing of up to 1 000 000 individual SNPs or more. Statistical power can also be limited by the typically small influence of an individual SNP on the outcome. Large cohorts are required to overcome these obstacles to identifying a statistically significant variant. At this time, very few GWASs for AR have been attempted.

In a candidate SNP analysis of 2724 SNPs and 990 kidney allograft recipients, no statistically significant SNPs were found to be associated with AR [10]. Multivariate models also failed to identify with any statistically significant SNPs, after accounting for a false discovery rate (FDR) of 10%, although many of the SNPs with the lowest *P*-values play a role in signaling pathways involved in T-cell activation. Additionally, some SNPs were associated with the severity of AR based on the *i* (*inflammation*) and *t* (*tubulitis*) scores on kidney allograft biopsy.

A larger-scale GWAS of 1528 European American renal allograft recipients and 450 130 SNPs again did not identify any statistically significant SNPs associated with AR [11]. SNPs with smallest *P*-values were rs146480420, within the epithelial cell adhesion molecule (*EPCAM*) gene, and rs59677415, near LOC102467213, both with a *P* value of $9e^{-7}$. The top 83 SNPs with smallest *P*-values were in the canonical pathways thought to impact AR such as NFkB activation, IL-8 signaling, and leukocyte extravasation signaling.

In a GWAS of European renal allograft recipients, the investigators used a pooled DNA approach consisting of 275 cases, 503 controls, and 1109 SNPs that were analyzed using a 50-kb sliding window to identify at least five contiguous SNPs for association with AR [12]. The pooled DNA approach reduces the number of tests needed which reduces cost. This method involves mixing equimolar amounts of DNA from each individual in the case or control groups and hybridizing the pools on a DNA-Bead Chip array [12], assaying, and then using statistical association tests for the genotypes between the case and control pools. DNA pooling approaches for association studies have been described elsewhere [13–15]. For validation, 313 cases and 531 controls were used to validate 14 SNPs. Two SNPs were identified as significantly associated with AR, one in *PTPRO*, coding for a receptor-type tyrosine kinase essential for B-cell receptor signaling and the second in the ciliary gene *CCDC67* [12]. Validation studies in other cohorts will be needed to confirm these two SNPs association with AR of kidney allografts.

For the aforementioned studies, only two SNPs were identified that were significantly associated with AR although there were also several SNPs just below the threshold of significance and were within pathways thought to impact AR. Reasons for these limited results are most likely due to the heterogeneity of AR where multiple pathways (and variants) may be associated with inducing or maintaining AR. This results in decreased statistical power and the ability to detect statistical significance. Additionally, it was shown that transplant center effects can greatly impact results and this may impact statistical associations when recipients from different transplant centers are combined into a single cohort [10]. This transplant center effect may also impact validation studies of candidate SNPs where independent cohorts are used to validate an initially reported variant. Furthermore, other clinical factors and genetic differences between populations can effect associations of genetics and AR, but are not always controlled for in studies. Thus, larger-scale, multicenter studies accounting for population stratification and clinical factors may lead to better identification of SNPs with significant association with AR.

At present, efforts are under way to expand the size of cohorts to be studied. The International Genetics & Translational Research in Transplantation Network (iGeneTRAiN) consortium [16,17] includes investigators from multiple studies to create a large cohort of different types of allograft recipients to overcome both the problem of multiple testing and the small impact of these SNPs. This group is currently conducting meta-analyses of AR from multiple cohorts where a GWAS has been performed. The primary advantage of meta-analysis is that studies can be combined to increase sample sizes and increase statistical power [17]. A disadvantage of combining GWAS across many clinical sites for such meta-analysis requires the centers to agree on specific endpoints and a common definition of AR. Additionally, the genetic data should be collected by similar methods and use of similar gene chips. If different GWAS chips are used by participating centers, genotypes can be imputed to a common variant set, although this requires additional bioinformatics steps prior to analysis. The iGeneTRAiN consortium has used imputed genotypes and common definitions of AR to conduct a robust meta-analysis of specific types of transplant and AR such as kidney.

More recent investigations are using DNA sequencing to identify rare SNPs which will be necessary to identify the genetic variances associated with AR which has not being identified through the analysis of common high allele frequency (AF) SNPs. These methods may lead to better understanding of the genetics of AR and possibly better therapy for the patients with AR.

Pharmacogenomics and acute rejection

To reduce the risk of AR, research has focused on optimizing immune suppression drugs following transplantation. Tacrolimus (TAC) is the primary immune suppressant used in >90% of kidney transplants to prevent AR and has differing efficacy in different populations, in large part due to the diverse rates of TAC metabolism, and has been the predominate focus of pharmacogenomics research in transplantation [18]. SNPs in the *CYP3A5* and *CYP3A4* drug metabolism genes, as well as TAC transporters, can influence the metabolic rates of TAC. Some of these SNPs, which impact the pharmacokinetics of TAC, lead to higher or lower dose requirements to achieve the therapeutic target. There is also evidence that high metabolic rates of immune suppressants in the blood, such as TAC [19] or cyclosporine [20], are associated with higher risk of AR. TAC and cyclosporine are transported by ABCB1 and metabolized by the CYP3A4 and CYP3A5 enzymes [21]. SNPs in the genes that express these, and related, enzymes have been the focus of most investigations of TAC trough blood concentrations and have been extensively reviewed elsewhere [22–24]. The *CYP3A5*3* SNP (rs776746) is the most commonly studied SNP and significantly decreases TAC metabolism [3,25] and the dose needed to reach therapeutic TAC blood concentrations. The *CYP3A5*3* SNP has inconsistently been associated with rejection [26,27]. Further studies have shown that combinations of SNPs affect TAC metabolism [28]. In a study of mainly Caucasian subjects, the effects of *ABCB1* SNPs on TAC concentrations were strongly accentuated by *CYP3A4* and *CYP3A5* genotype [29] although this has been inconsistently shown. Some studies have shown that the **28* SNP in the cytochrome P450 oxidoreductase gene (*POR*) is associated with increased metabolic activity of CYP3A4 and CYP3A5 [30]. Subjects with rapid TAC-metabolizing SNPs such as *CYP3A5*1 and POR*28T* when compared with slow-metabolizing *CYP3A5*3 and CYP3A4*22* SNPs have dose requirements two to three times greater and a significantly longer time to reach therapeutic trough blood concentrations. However, no differences were observed in AR by SNP genotype [31]. Another study suggested that SNPs in the *POR*, *ABCB1* and *CYP3A5* genes should all be considered when dosing TAC [32]. Optimal

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dosing of immune suppressants may lead to lower rates of AR.

The *CYP3A5* SNPs important in TAC metabolism differ significantly by race. SNP frequencies in many genes have been found to vary between different world populations [33] and may cause variability in response to drugs including TAC [34], which is similar to what was discovered about cyclosporine in the 1990s [20]. The *CYP3A5*3* loss-of-function (LoF) SNP causes alternative RNA splicing [35,36] resulting in mRNA decay [37] and loss of TAC metabolic activity [38]. The *CYP3A5 *1* (functional) and **3* (LoF) SNPs have been validated by *in vitro* experiments using CRISPR/Cas9 genetic engineering of the *CYP3A5* gene in cell lines and TAC metabolism assays [38]. This **3* LoF SNP has an AF of >90% in Caucasians but only around 14% in sub-Saharan Africans [39]. African Americans also carry the *CYP3A5 *6* and **7* SNPs with AFs = 10–22% [40], which also result in low CYP3A5 enzyme activity but are extremely rare in Caucasians. Therefore, nearly all Caucasians will have low capacity for TAC metabolism. However, TAC metabolism in people of African descent is highly unpredictable as some will have low, intermediate, or high metabolic rates of TAC. A recent GWAS showed definitively that TAC trough concentrations were tightly associated with *CYP3A5*3*, **6* and **7* SNPs in African Americans [3] and a dosing model for the prediction of TAC dose using these genotypes has been developed to facilitate clinical implementation [41]. In addition, the Clinical Pharmacogenomic Implementation Consortium (CPIC) has published guidelines for genotype-guided TAC dosing [42]. Genotype-based dosing of TAC has a potential to improve management of TAC which could lead to better outcomes and reduction in AR rates.

The association between AR and intrapatient variability in TAC concentration has been the subject of many recent papers. Causes of intrapatient TAC variability in trough concentrations are multifactorial including genetics, diarrhea, drug–drug interactions, nonadherence, or generic TAC substitution [43]. High intrapatient variability in TAC blood concentrations was associated with increased risk of AR [44]. TAC intrapatient variability was significantly associated with kidney AR, but the TAC intrapatient variability was not explained by the *CYP3A5*3* genotype alone [45], suggesting that other genetic variants and clinical factors may be important. Other studies have shown that high TAC intrapatient variability in blood concentrations is associated with poorer short- and long-term outcomes and biopsy histology post-transplant [46–49]. Studies have shown that high TAC intrapatient trough variability led to increased rates of late rejection and graft loss in pediatric kidney allografts [50,51]. Also, the once-daily TAC formulation, despite potential of improving adherence, did not reduce the high TAC intrapatient trough variability compared with the twice-daily dosing [52]. As many of the immune suppressants used in transplantation are impacted by metabolic and transport genes, and also target similar immunological and pharmacogenetic pathways, proper dosing is important. Dosing that reduces intrapatient variability in immune suppressant blood concentrations may lead to improved outcomes. Currently, there are no trials of genotype-based dosing to reduce intrapatient trough TAC variability. Genotype-based TAC dosing trials are needed, especially for the African Americans who are prone to under-dosing, in large part due to higher frequencies of SNPs associated with higher rates of TAC metabolism.

In the future, we envision implementing genotype-based dosing models for TAC that account for genetic and clinical factors. The goal of dosing models would be to reach therapeutic TAC concentration early and to maintain the optimal troughs following transplantation. One such dosing equation determined that the *CYP3A5*1* genotype and four clinical factors were important for TAC clearance [53]. Another study developed a TAC dosing model for African American kidney transplant recipients [41]. These studies were limited to common genotypes and future dosing models will need to include low-frequency variants identified from next-generation sequencing studies and possibly include epigenetics and more clinical factors. We foresee genetic-based TAC dosing as a method that can improve transplant outcomes and possibly reduce rates of AR through optimized immune suppression.

Future directions in transcriptomics

Beyond genotype-based dosing and SNPs that have been associated with AR, variation in gene expression has also been evaluated to predict the risk of AR. Gene expression can also be used as a method to better define subtypes of AR. Global gene expression, known as transcriptomics, can be used to investigate the total RNA expressed in a tissue at a given time by microarray or RNA sequencing (RNAseq). These studies use markers in the blood of transplant patients or in the biopsy with the objective of understanding whether gene expression profiles can be used to predict transplant outcomes or how to better treat episodes of AR. Studies conducted

primarily by the laboratories of Drs. Philip Halloran [54–77] and Minnie Sarwal [78–83] report differences in gene expression profiles in cells taken from of an extra kidney biopsy core, or blood, can predict the risk of TCMR and ABMR. Studies show improvement in TCMR and better risk stratification for allograft loss among recipients with ABMR [77]. Unfortunately, obtaining this extra biopsy core is not always feasible in the clinical setting, limiting clinical implementation. Most transcriptomic studies in transplantation have used microarray chips that detect only known gene segments that are customized on a chip. In contrast, newer technology such as RNAseq can determine the presence of RNA expression from the entire gene, partial gene segments, and some isoforms of genes and also can quantify the level of gene expression. RNAseq is becoming the preferred method to detect global gene expression and could be useful in AR association studies to determine AR pathology, classification, risk, and possibly AR therapy.

Transcriptomic studies in the blood of renal allograft patients have been used to predict risk for AR. Our team published an RNA profile, over time, using RNAseq from a cohort of immunosuppressed kidney allograft recipients that did not undergo AR that can be used as a baseline transcriptomic RNAseq signature [84]. Similar studies have been performed with microarray to develop a signature for renal transplant tolerance [85,86]. Other studies have used gene profiling from blood [87] using microarray to study gene expression profiles of AR. Molecular markers in blood could also be used to detect AR and AR risk such as specific mRNAs, proteins, free DNA, or metabolites [2]. It has also been reported that donor-derived cell free DNA in the blood can be used as a marker for active AR of kidney allografts [88]. Furthermore, the kSORT assay has been developed to test expression of specific genes in blood for AR risk [89,90]. Although gene expression testing of renal allograft function, and risk for AR, in blood is minimally invasive, further studies have been conducted to understand AR in renal allograft biopsy tissue where rejection actively occurs.

Gene expression analysis of biopsies can be used, along with histology and Banff scores, to better define, classify, and detect the types of AR. A recent publication following the XIII Banff meeting has begun the discussion of how to use transcriptomics as a method to classify AR [2]. To this point, a number of studies aimed to better understand AR using transcriptomics in biopsy tissue. One study showed that expression analysis of dysregulated gene pathways in renal allograft biopsies with interstitial fibrosis and tubular atrophy, but no histological evidence of inflammation, has been shown to be a sensitive method to detect future graft loss [91]. When histology of biopsies is ambiguous, pathologists do not always agree on the diagnosis; thus, molecular analysis can be useful. Using microarray results from 403 kidney transplant biopsies, a microarray probe set was used to determine TCMR scores [74]. The TCMR scores, in the study, had an accuracy rate of 89% in concordance with histology which includes TCMR and mixed; the primary disagreements were when histology was ambiguous ("borderline") [74]. In a study of 403 biopsies, of the 45 biopsies that were diagnosed as ABMR by gene expression, 39 were diagnosed as ABMR by histology and donor-specific antibodies; the ABMR gene expression score strongly predicted graft loss [75]. These gene expression diagnostic studies were further validated by an international prospective study (INTERCOM) investigating 300 new biopsies from six centers [62,63]. The INTERCOM study determined that the ABMR scores agreed with conventional assessment at an accuracy rate of 85% [62]. The INTERCOM study also determined that gene expression TCMR diagnosis accuracy rate was 87% compared with histological diagnosis that included both TCMR and mixed rejection [63]. However, 77 of the 300 biopsies were further reclassified with 16 histologically TCMR and molecularly non-TCMR, 15 histologic non-TCMR were molecularly TCMR, while all 46 "borderline" biopsies by histology were reclassified with 8 TCMR or 38 non-TCMR. Thus, gene expression diagnosis of biopsies can be used to further classify ambiguous, borderline, and mixed rejection. Taken together, transcriptomics has potential to aid in the molecular classification and definition of specific types of AR that could be used in concordance with standard histological and clinical AR diagnostics.

In summary, this literature review shows numerous genetic variants that have been associated with AR in kidney transplantation. Many of these genetic variants' associations with AR require larger studies, meta-analysis, and subsequent validation. Furthermore, there are large amounts of intrapatient variability in TAC concentrations in the blood of the kidney recipients that have been linked to AR. Dosing equations that incorporate genetic variants and clinical factors to personalize the TAC dose may be able to reduce the

intrapatient variability in blood concentrations and achieve stable and therapeutic concentrations effectively. Additionally, understanding the RNA expression signatures in kidney transplant recipients may lead to better diagnosis, classification, and treatment of AR, based on gene expression. Thus, we think genetics will continue to play an important role in the future of diagnosing, defining, and treating AR in kidney transplant recipients.

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Conflict of Interest

The authors declare no conflicts of interest.

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