Published in final edited form as:

Curr Opin Organ Transplant. 2020 February ; 25(1): 35–41. doi:10.1097/MOT.0000000000000718.

Genetic Background and Transplantation Outcomes: Insights from GWAS

Francesca Zanoni¹, Krzysztof Kiryluk¹

¹Department of Medicine, Division of Nephrology, Columbia University, College of Physicians & Surgeons, New York, USA.

Abstract

Purpose of Review: This review summarizes recent advances in the genetic studies of transplantation outcomes, including new genome-wide association studies for acute rejection, allograft survival, pharmacogenomics, and common transplant comorbidities.

Recent findings: Genetic studies of kidney transplantation outcomes have begun to address the question of non-HLA genetic compatibility, including the role of genome-wide mismatches in missense variants, and the “genomic collision” hypothesis under which the risk of rejection may be increased in recipients homozygous for loss-of-function variants with grafts from non-homozygous donors. In recent pilot studies, missense mismatch scores for transmembrane and secreted proteins were associated with antibodies against the mismatched peptides and reduced allograft survival. A “genomic collision” at the *LIMS1* locus involving a common deletion near *LIMS1* gene was associated with anti-LIMS1 antibody response and increased risk of rejection. Additional genetic factors under active investigation include genome-wide polygenic risk scores for renal function and *APOL1* risk genotypes in African American kidney donors. Due to the heterogeneity and complexity of clinical outcomes, new GWAS discoveries for rejection, allograft survival, and specific transplant comorbidities will require larger multi-center meta-analyses.

Summary: Genetic compatibilities between donor and recipient represent an important determinant of rejection and long-term allograft survival. Genetic background of transplant donors may be additionally predictive of allograft function, while recipient’s genomes are likely determinant of a wide range of transplantation outcomes, from rejection susceptibility to pharmacogenetics and various comorbidities related to prolonged immunosuppression.

Keywords

genome-wide association studies (GWAS); exome sequencing; genetic mismatch; genomic collision; rejection; allograft survival; kidney transplant

Introduction

Genetic factors contribute to a wide range of transplantation outcomes, from rejection and complications of prolonged immunosuppression to allograft failure and mortality (1). Genetic mismatches at human leukocyte antigen (HLA) genes have been studied extensively as independent predictors of rejection and graft survival (2). However, rejection can occur even in the setting of perfect HLA matching (3), and it has been estimated that only 1 in 5 graft losses are directly attributable to HLA mismatch (4). This suggests an important role of additional, yet undefined genetic factors in the determination of immune-related outcomes. Similarly, genetic determination of non-immune risk factors is poorly understood, including the impact of inherited risk for cardiovascular disease, diabetes, infection, or malignancy in the setting of prolonged immunosuppression.

Over the past decade, GWAS has proven utility in shedding light into the human biology of many multifactorial traits. However, the application of GWAS to transplant outcomes has been slow, mainly due to the lack of adequately powered genetic cohorts with genome-wide genotype or sequence data. In this review, we will summarize recent applications of GWAS to transplantation outcomes, including studies of genetic mismatch between donors and recipients, investigations linking donor genetics with allograft survival, and studies testing recipient-specific genetic factors for association with alloimmunity, pharmacogenomics, and susceptibility to immunosuppression-related comorbidities (Figure 1).

Donor-recipient mismatch

Genetic studies of alloimmunity represent a particularly challenging area, mainly because the relevant outcomes are often determined by composite effects of genetic interactions between donor and recipient genomes, and a multitude of other medical and surgical factors. Prior candidate gene studies have suggested several mismatches outside HLA that may cause ligand-receptor incompatibilities between donor and recipient, or production of antibodies against non-HLA antigens, so called minor histocompatibility antigens (MHA). It has been hypothesized that anti-MHA antibodies are likely targeting antigens that are most exposed to the immune system, either because they are expressed on cell surfaces (especially by the vascular endothelial cells), or because they are released from apoptotic and necrotic cells during ischemic injury at the time of transplantation (5,6).

Several studies described antibodies specifically directed against MHC class I polypeptide-related sequence A (MICA) that were associated with poor graft outcomes (7–9). *MICA* gene is highly polymorphic and encoded within the MHC region, complicating the precise genetic dissection of this locus. Other examples of anti-MHA response associated with allograft injury include antibodies directed against angiotensin II type 1 receptor (AT1R) or endothelin-1 type A receptor (ETAR), both expressed by renal endothelial cells (10–13). A different class of genetic incompatibility is exemplified by mismatches in recipient's killer-cell immunoglobulin-like receptors (KIRs) and donor's ligands (HLA-C) that could result in ligand-receptor pairings perpetuating NK-mediated cytotoxic injury, although the role of such mismatches requires further validation (14,15). In addition, epidemiological studies suggested that donor-recipient sex mismatch is associated with poor outcomes, and serologic

studies in female recipients of male organs identified antibodies directed against chromosome Y-encoded proteins (16–18). Notably, sex mismatch has also been identified as a risk factor for graft-versus-host disease in the setting of a female-to-male hematopoietic stem cell transplant (19,20).

Genome-wide association studies (GWAS) of donor-recipient pairs represent an unbiased approach that could be used to identify novel incompatibility loci by formally testing various types of donor-recipient interactions genome-wide. Such genome-wide studies can be further enhanced by high throughput serum antibody screening that could, when combined with genetic evidence, provide orthogonal support for novel MHAs. Given the complexity and heterogeneity of rejection outcomes, large cohorts with complete clinical data, donor and recipient DNA, and serum sampled preferably at the time of rejection are needed for the success of such studies.

Genetic donor-recipient interactions

To date, there has been only one GWAS combining the analysis of kidney donors and recipients. This study was carried out by the Wellcome Trust Case Control Consortium (WTCCC) in a two-phase design, including 2,094 kidney donor-recipient pairs in the discovery and additional 5,866 pairs in the replication phase (21*). Several models were tested, including donor-only and recipient-only GWAS, but donor-recipient interaction models and donor-recipient mismatches in copy number variants were also examined. The outcomes tested were time to acute rejection and graft failure. No statistically significant signals outside HLA were found under any of the tested models, stressing the complexities of the research question and the challenges related to the heterogeneity of outcomes.

One of the major limitations of this study was that the phenotypes were assessed retrospectively from registry data and were not homogeneously defined. Moreover, the discovery phase was still small by GWAS standards, and likely insufficient to detect more complex genotypic interactions or genetic variants with smaller effects. The International Genetics & Translational Research in Transplantation Network (iGeneTRAiN) consortium was formed to specifically address these limitations (22,23). The consortium has laid the groundwork for larger multicenter GWAS meta-analyses by designing a custom SNP chip with increased coverage of HLA and alloimmunity-relevant loci (24), and by broadly engaging all of the existing genetic cohorts in worldwide collaborative efforts.

The missense hypothesis

Based on the assumption that MHAs are products of allograft-expressed genes that carry non-synonymous single-nucleotide polymorphisms (nsSNPs), a mismatch in nsSNPs between donors and recipients has been hypothesized to increase the risk of graft rejection and failure (25). A recent study tested this hypothesis in 477 kidney donor-recipient pairs genotyped with the iGeneTRAiN SNP chip (26**). The study restricted the analysis to 59,268 nsSNPs in the genes encoding transmembrane or secreted proteins under the assumption that such proteins were more likely to be exposed to the immune system after transplant. The count of mismatched alleles (defined as any donor allele that is absent in the recipient) was independently associated with graft failure after adjustment for HLA

mismatch and relevant clinical covariates, but the outcome of rejection was not directly tested. The use of the count of mismatched alleles as a cumulative risk predictor allowed to overcome the power limitation, but the model did not account for differences in potential immunogenicity between amino acid substitutions, did not model linkage disequilibrium (LD) between variants, and the variant effects were not assessed individually to prioritize potential drivers of this association. Interestingly, in 25 patients with chronic antibody-mediated rejection and available sera, 16 had donor-specific antibodies directed against genetically mismatched transmembrane proteins as detected by protein arrays. Although these findings are promising, the pathogenic role of these antibodies is still unclear and the genetic model awaits further replication in external donor-recipient cohorts.

A reverse mismatch hypothesis has also been explored by GWAS for graft-versus-host disease (GVHD) in the setting of hematopoietic stem cell transplantation (27,28). Sato-Otsubo et al (27) described two non-HLA loci associated with acute GVHD risk in an HLA-restricted analysis of donor-recipient allelic mismatches. Martin et al (28) reported that a cumulative genome-wide mismatch for variants within coding regions was associated with GVHD. The missense hypothesis has also been explored using exome sequencing in two small kidney transplant pilot studies. The first study involved exome analysis of 53 living kidney donor-recipient pairs and suggested an association of donor-recipient mismatch score in transmembrane proteins with lower eGFR at 3 years (29). Pineda et al (30) studied 28 kidney donor-recipient pairs and described a higher level of missense mismatch exome-wide in cases of rejection compared to those with stable graft function. These findings have not yet been replicated in independent cohorts.

In summary, the missense hypothesis is now testable with SNP arrays or exome sequencing, but adequately powered genetic studies are still needed to validate these recent observations. Additional work is also needed to improve mismatch scoring methods that should account for LD and potential differences in immunogenicity of individual amino acid substitutions.

The loss-of-function hypothesis

“Genomic collision” refers to a situation in which a gene-disrupting variant in homozygosity is found in a recipient, but not in the donor, potentially leading to allorecognition if the intact gene product in the allograft. Given a high frequency of loss-of-function variants in human nonessential genes (31), the “genomic collision” may represent a common unrecognized cause of allosensitization.

A recent study investigated the role of common gene-disrupting deletions inherited in homozygosity by the recipient (32*). In the discovery phase, 50 deletion-tagging SNPs were screened for association with biopsy-confirmed rejection in 705 kidney allograft recipients. A homozygous variant at the chromosome 2q12.3 locus was found to be associated with rejection independently of HLA mismatch and other clinical risk factors. This variant was next tested under the “genomic collision” model in three additional cohorts totaling 2004 donor-recipient pairs. The “collision genotype” at this locus, defined as a specific donor-recipient genotype combination in which a recipient who was homozygous for a deletion-tagging allele received a transplant from a non-homozygous donor, was associated with a higher risk of rejection in all three replication cohorts. The tested variant resided in the

intronic portion of *LIMS1* gene that encodes a protein involved in cell adhesion and integrin signaling. This protein is expressed in the glomerulus, distal tubular compartment, as well as in the glomerular and vascular endothelium, and its cell surface expression was induced by hypoxia. The risk variant tagged a common 1.5-kb deletion downstream of *LIMS1*, and was associated with lower kidney mRNA levels of *LIMS1*. Moreover, the collision genotype was associated with the presence of anti-LIMS1 antibodies detected by protein arrays and confirmed by ELISA. These findings provided support for the hypothesis that the “collision genotype” led to anti-LIMS1 response directed against ischemia-induced LIMS1 in high-risk donor-recipient pairs. Nevertheless, these findings will still require validation in renal and non-renal transplant setting, and further corroboration by functional studies to demonstrate the pathogenicity of anti-LIMS1 antibodies.

In summary, the “genomic collision” model is tractable using GWAS or sequencing approaches, and can be expanded to all types of loss-of-function variants genome-wide. Similar to the missense hypothesis, this model may be broadly applicable to all types of transplanted organs, but testing its generalizability and clinical utility requires additional studies.

Donor's Genetic Background

APOL1 genotype

The *APOL1* kidney risk genotypes are inherited in up to 15% of individuals of African ancestry (33). Several retrospective studies suggested that donor *APOL1* risk genotypes were associated with worse allograft outcomes (34–36), whereas recipient risk genotypes were not correlated with graft survival (37). These findings are consistent with the hypothesis that *APOL1*-related injury depends on kidney expression of the altered *APOL1* protein (38), and may partially explain the observation that kidneys from African American donors are associated with higher risk of allograft failure (39). Moreover, a recent retrospective study showed rapid decline of eGFR and increased risk of ESRD among donors with the risk genotype (40), raising serious concerns about donation safety in *APOL1* risk genotype carriers (41). A prospective multicenter study called APOLLO is underway to assess the effect of *APOL1* on both living donor and recipient outcomes (42).

In summary, *APOL1* illustrates an important and common genetic factor that is ancestry-specific, appears to have a large effect on the risk of graft loss, and may also affect the safety of kidney donation. Future donor-based GWAS approaches may be able to identify additional genetic risk factors that affect donation risks and allograft function, including potential genetic modifiers of the *APOL1* risk.

Polygenic risk

Genome-wide polygenic risk scores (PRS) leverage the existing GWAS findings to capture the cumulative effect of all common variants across the genome in determining disease risk. Recent studies demonstrate that individuals in the top 5% of PRS distribution may have disease risk equivalent to many of the rare variants currently tested for clinically (43). For example, a genome-wide polygenic risk score for BMI has been developed and validated

that uses 2.1 million common genetic variants to accurately predict the development of severe obesity (44). With the availability of large scale GWAS for renal function, PRS may become useful tools for prediction of kidney disease (45). The application of PRS in the setting of kidney transplant could be of potential value in predicting long-term allograft function and the renal risks after donation.

Recent study evaluated the performance of a genome-wide PRS in predicting allograft function in 10,844 donor-recipient pairs (46). The PRS was expressed as an effect size-weighted sum of independent risk alleles that reached P-value of less than 1×10^{-4} in the recent population-based GWAS for kidney function (47). This score was applied to donors as well as recipients to predict allograft function at 1 and 5 years, and change in eGFR post-transplant. Interestingly, the donor PRS was not significantly associated with allograft function, but the recipient PRS appeared to be associated with eGFR at 1-year post-transplant. However, the effect sizes of the recipient PRS were negligible compared to the traditional clinical predictors. These unexpected findings suggested that the PRS formulation used may be more reflective of non-renal genetic factors affecting eGFR, such as the rate of Cr production (e.g. muscle mass), or susceptibility to systemic conditions affecting renal function (e.g. diabetes). Neither donor or recipient PRS had significant associations with a 5-year post-transplant eGFR nor the change in graft function over 5 years.

In summary, the application of PRS approach to allograft function has not resulted in a clinically meaningful prediction to date. However, this approach is only going to get more powerful as the methods to model PRS are improving (48), and larger GWAS studies for CKD continue to emerge (49).

Recipient's Genetic Background

Acute rejection and allograft function

The first recipient-only GWAS for kidney allograft survival involved 326 European transplants (50), but no loci reached genome-wide significance and the two suggestive loci were not confirmed by a subsequent validation (51). Another underpowered recipient GWAS used a DNA pooling approach to analyze 275 European cases of T-cell mediated rejection and 503 controls in the discovery phase (52). The study described two loci, but they were not genome-wide significant by GWAS standards and failed to replicate in external cohorts (53). These small studies were followed by the WTCCC GWAS with the discovery in 2686 kidney recipients (21*). None of the loci reached genome-wide significance, or validated in the replication phase that involved another 5866 additional recipients. Although this is the largest study to date, its power is relatively low in comparison to other successful GWAS studies for immune-related traits.

In summary, these early studies clearly demonstrate the need for larger genetic cohorts with longer clinical follow up and more granular phenotypes in order to maximize the power for genetic discovery.

Pharmacogenomics

Calcineurin inhibitors, a broadly used class of immunosuppressants, have a narrow therapeutic window that is monitored with blood concentration measurements. Among them Tacrolimus (TAC) is metabolized through the cytochrome P450 proteins encoded by *CYP3A4* and *CYP3A5*. There is a high level of inter-individual variability in TAC blood trough levels, and common loss-of-function variant in *CYP3A5**3 allele is known to affect TAC metabolism (54,55). Two recent GWAS were conducted to assess genetic factors associated with dose-adjusted TAC levels in African American and European kidney transplant recipients (56,57). Both studies confirmed that *CYP3A5* is the main genetic locus controlling TAC troughs. Three common loss-of-function variants (*CYP3A5**3, 6, and 7) explained ~16–34% of variance in troughs in African Americans, while *CYP3A5**3 and a reduced function variant *CYP3A4**22 jointly explained ~16% of variance in Europeans. An expanded GWAS combining data for 1948 Europeans and 391 African Americans did not discover any new variants beyond the *CYP3A5/A4* locus (58). Additionally, several TAC- and mycophenolate-associated adverse events were studied (nephrotoxicity, diabetes, anemia and leukopenia), but no genome-wide significant associations were found (58).

These findings demonstrated that most of the genetic variance in TAC metabolism lies in *CYP3A5/A4* genes, although larger GWAS in more diverse ancestries may be able to identify additional genetic variants associated with TAC pharmacokinetics and toxicity. Importantly, the observed effects of *CYP3A5* variants are large and clinically meaningful; interventional studies of personalized TAC dosing are now needed to assess the clinical utility these variants.

Transplant comorbidities

With increasing average age of transplant recipients, the immunosuppression-related comorbidities are becoming major determinants of graft and patient survival (4). These comorbidities, including cardiometabolic disease and cancer, are known to have strong genetic basis in non-transplant population (59–62). However, the interaction of inherited risk factors with the effects of prolonged immunosuppression are not well studied. To date, only two small GWAS of post-transplant complications were performed, one for new-onset diabetes after transplantation (63), and another one for non-melanoma skin cancers (64). Neither one was powered sufficiently to support genetic associations at the level of genome-wide significance.

Considering that powerful GWAS for cardiovascular disease, diabetes, and cancer are already available, the PRS approach may be potentially useful for risk stratification in the transplant setting. For example, an early formulation of a PRS for cardiovascular disease based on the 27 GWAS-discovered SNPs was significantly associated with major cardiovascular events in a cohort of 1,640 kidney transplant recipients from the ALERT trial (65). Similarly, the PRS models based on GWAS for basal cell and squamous cell carcinomas were found to be significantly predictive of skin cancers among 889 European kidney transplant recipients (66). As GWAS studies for these traits are becoming larger and more predictive across diverse ancestries, we anticipate that future studies will test the

clinical utility of newer PRS formulations in the setting of transplant, further exploring their interactions with long-term immunosuppression.

Conclusions and Future Perspective

Modern GWAS and sequencing approaches offer powerful tools for genetic investigations of immune and non-immune factors affecting allograft outcomes. Systematic analysis of genetic mismatches between donors and recipients in large cohorts will be needed for the refinement and validation of the missense and loss-of-function hypotheses. GWAS approaches combined with high throughput serum antibody screening are likely to accelerate the discovery of novel MHAs. More powerful genome-wide formulations of polygenic predictors may potentially provide actionable tools for risk stratification, but rigorous validation studies will be needed across diverse ancestries and transplant settings to assess their clinical utility. Moreover, larger multicenter efforts are still needed to enable high-quality donor and recipient GWAS to uncover precise genetic mechanisms underlying rejection, allograft survival, and transplant comorbidities.

Acknowledgements:

This work was supported by the Columbia Transplant Center, Columbia University, New York and the following NIH grants: Columbia Clinical and Translational Science Award grant UL1TR001873 from the National Center for Advancing Translational Sciences (NCATS), Electronic Medical Records and Genomics (eMERGE) Network grant U01HG8680 from the National Human Genome Research Institute (NHGRI), APOL1 Long-Term Kidney Transplantation Outcomes Network (APOLLO) grant U01DK116066, and Columbia Kidney Precision Medicine Project (KPMP) grant UH3DK114926 from the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK). Francesca Zanoni is additionally supported by a research fellowship stipend from the University of Milan, Italy.

References

1. Yang JYC, Sarwal MM. Transplant genetics and genomics. *Nat Rev Genet.* 2017;18(5):309–326. doi:10.1038/nrg.2017.12 [PubMed: 28286337]
2. Held PJ, Kahan BD, Hunsicker LG, et al. The Impact of HLA Mismatches on the Survival of First Cadaveric Kidney Transplants. *N Engl J Med.* 1994;331(12):765–770. doi:10.1056/NEJM199409223311203 [PubMed: 8065404]
3. Sigdel TK, Li L, Tran TQ, et al. Non-HLA Antibodies to Immunogenic Epitopes Predict the Evolution of Chronic Renal Allograft Injury. *J Am Soc Nephrol.* 2012;23(4):750–763. doi:10.1681/ASN.2011060596 [PubMed: 22302197]
4. Terasaki PI. Deduction of the fraction of immunologic and non-immunologic failure in cadaver donor transplants. *Clin Transpl.* 2003;449–452. <http://www.ncbi.nlm.nih.gov/pubmed/15387129>. Accessed September 2, 2019. [PubMed: 15387129]
5. Yang JYC, Sigdel TK, Sarwal MM. Self-antigens and rejection. *Curr Opin Organ Transplant.* 2016;21(4):362–367. doi:10.1097/MOT.0000000000000328 [PubMed: 27214090]
6. Subramanian V, Mohanakumar T. Chronic rejection: a significant role for Th17-mediated autoimmune responses to self-antigens. *Expert Rev Clin Immunol.* 2012;8(7):663–672. doi:10.1586/eci.12.58 [PubMed: 23078063]
7. Sumitran-Holgersson S, Wilczek HE, Holgersson J, Söderström K. Identification of the nonclassical HLA molecules, mica, as targets for humoral immunity associated with irreversible rejection of kidney allografts. *Transplantation.* 2002;74(2):268–277. doi:10.1097/00007890-200207270-00019 [PubMed: 12151741]
8. Mizutani K, Terasaki P, Bignon JD, et al. Association of Kidney Transplant Failure and Antibodies Against MICA. *Hum Immunol.* 2006;67(9):683–691. doi:10.1016/j.humimm.2006.06.002 [PubMed: 17002898]

9. Zou Y, Stastny P, Süsal C, Döhler B, Opelz G. Antibodies against MICA antigens and kidney-transplant rejection. *N Engl J Med.* 2007;357(13):1293–1300. doi:10.1056/NEJMoa067160 [PubMed: 17898098]
10. Amico P, Hönger G, Biemann D, et al. Incidence and Prediction of Early Antibody-Mediated Rejection due to Non-Human Leukocyte Antigen-Antibodies. *Transplantation.* 2008;85(11):1557–1563. doi:10.1097/TP.0b013e31816f612a [PubMed: 18551059]
11. Dragun D, Müller DN, Bräsen JH, et al. Angiotensin II Type 1–Receptor Activating Antibodies in Renal-Allograft Rejection. *N Engl J Med.* 2005;352(6):558–569. doi:10.1056/NEJMoa035717 [PubMed: 15703421]
12. Banasik M, Boratyska M, Kościńska-Kasprzak K, et al. Non-HLA Antibodies: Angiotensin II Type 1 Receptor (Anti-AT1R) and Endothelin-1 Type A Receptor (Anti-ETAR) Are Associated With Renal Allograft Injury and Graft Loss. *Transplant Proc.* 2014;46(8):2618–2621. doi:10.1016/j.transproceed.2014.09.029 [PubMed: 25380879]
13. Jackson AM, Sigdel TK, Delville M, et al. Endothelial Cell Antibodies Associated with Novel Targets and Increased Rejection. *J Am Soc Nephrol.* 2015;26(5):1161–1171. doi:10.1681/ASN.2013121277 [PubMed: 25381426]
14. van Bergen J, Thompson A, Haasnoot GW, et al. KIR-ligand mismatches are associated with reduced long-term graft survival in HLA-compatible kidney transplantation. *Am J Transplant.* 2011;11(9):1959–1964. doi:10.1111/j.1600-6143.2011.03621.x [PubMed: 21714849]
15. Tran TH, Unterrainer C, Fiedler G, et al. No impact of KIR-ligand mismatch on allograft outcome in HLA-compatible kidney transplantation. *Am J Transplant.* 2013;13(4):1063–1068. doi:10.1111/ajt.12134 [PubMed: 23398855]
16. Gratwohl A, Döhler B, Stern M, Opelz G. H-Y as a minor histocompatibility antigen in kidney transplantation: a retrospective cohort study. *Lancet (London, England).* 2008;372(9632):49–53. doi:10.1016/S0140-6736(08)60992-7
17. Kim SJ, Gill JS. H-Y Incompatibility Predicts Short-Term Outcomes for Kidney Transplant Recipients. *J Am Soc Nephrol.* 2009;20(9):2025–2033. doi:10.1681/ASN.2008101110 [PubMed: 19541808]
18. Tan JC, Wadia PP, Coram M, et al. H-Y Antibody Development Associates With Acute Rejection in Female Patients With Male Kidney Transplants. *Transplantation.* 2008;86(1):75–81. doi:10.1097/TP.0b013e31817352b9 [PubMed: 18622281]
19. Loren AW, Bunin GR, Boudreau C, et al. Impact of Donor and Recipient Sex and Parity on Outcomes of HLA-Identical Sibling Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2006;12(7):758–769. doi:10.1016/j.bbmt.2006.03.015 [PubMed: 16785065]
20. Spierings E, Kim Y-H, Hendriks M, et al. Multicenter Analyses Demonstrate Significant Clinical Effects of Minor Histocompatibility Antigens on GvHD and GvL after HLA-Matched Related and Unrelated Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant.* 2013;19(8):1244–1253. doi:10.1016/j.bbmt.2013.06.001 [PubMed: 23756210]
- 21 *. Hernandez-Fuentes MP, Franklin C, Rebollo-Mesa I, et al. Long- and short-term outcomes in renal allografts with deceased donors: A large recipient and donor genome-wide association study. *Am J Transplant.* 2018;18(6):1370–1379. doi:10.1111/ajt.14594. [PubMed: 29392897] This is the largest GWAS for acute rejection and long-term kidney allograft failure published to date that systematically assessed donor genetics, recipient genetics, and donor-recipient genetic interactions as predictors of transplantation outcomes.
22. International Genetics & Translational Research in Transplantation Network (iGeneTRaIN). Design and Implementation of the International Genetics and Translational Research in Transplantation Network. *Transplantation.* 2015;99(11):2401–2412. doi:10.1097/TP.0000000000000913 [PubMed: 26479416]
23. Fishman CE, Mohebbasab M, Van Setten J, et al. Genome-Wide Study Updates in The International Genetics & Translational Research in Transplantation Network (iGeneTRaIN). *Front Genet.* 2019;10:1084. doi:10.3389/FGENE.2019.01084 [PubMed: 31803228]
24. Li YR, Van Setten J, Verma SS, et al. Concept and design of a genome-wide association genotyping array tailored for transplantation-specific studies. 2011. doi:10.1186/s13073-015-0211-x

25. Roopenian D, Choi EY, Brown A. The immunogenomics of minor histocompatibility antigens. *Immunol Rev.* 2002;190:86–94. <http://www.ncbi.nlm.nih.gov/pubmed/12493008>. Accessed August 30, 2019. [PubMed: 12493008]
- 26 **. Reindl-Schwaighofer R, Heinzel A, Kainz A, et al. Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: genome-wide analysis in a prospective cohort. *Lancet (London, England).* 2019;393(10174):910–917. doi:10.1016/S0140-6736(18)32473-5 This study was the first to test the missense hypothesis in a genome-wide fashion -- the cumulative sum of non-synonymous mismatches in transmembrane and secreted proteins was associated with shorter kidney graft survival.
27. Sato-Otsubo A, Nannya Y, Kashiwase K, et al. Genome-wide surveillance of mismatched alleles for graft-versus-host disease in stem cell transplantation. *Blood.* 2015;126(25):2752–2763. doi:10.1182/blood-2015-03 [PubMed: 26432889]
28. Martin PJ, Levine DM, Storer BE, et al. Genome-wide minor histocompatibility matching as related to the risk of graft-versus-host disease. *Blood.* 2017;129(6):791–798. doi:10.1182/blood-2016-09-737700 [PubMed: 27872059]
29. Mesnard L, Muthukumar T, Burbach M, et al. Exome Sequencing and Prediction of Long-Term Kidney Allograft Function. *Peters B, ed. PLOS Comput Biol.* 2016;12(9):e1005088. doi:10.1371/journal.pcbi.1005088 [PubMed: 27684477]
30. Pineda S, Sigdel TK, Chen J, Jackson AM, Sirota M, Sarwal MM. Novel Non-Histocompatibility Antigen Mismatched Variants Improve the Ability to Predict Antibody-Mediated Rejection Risk in Kidney Transplant. *Front Immunol.* 2017;8:1687. doi:10.3389/fimmu.2017.01687 [PubMed: 29259604]
31. Sulem P, Helgason H, Oddson A, et al. Identification of a large set of rare complete human knockouts. *Nat Genet.* 2015;47(5):448–452. doi:10.1038/ng.3243 [PubMed: 25807282]
- 32 *. Steers NJ, Li Y, Drace Z, et al. Genomic Mismatch at LIMS1 Locus and Kidney Allograft Rejection. *N Engl J Med.* 2019;380(20):1918–1928. doi:10.1056/NEJMoa1803731 [PubMed: 31091373] This kidney transplant genetic study tested the “genomic collision” hypothesis using a set of common deletions and discovered LIMS1 as a potential novel minor histocompatibility antigen.
33. Genovese G, Friedman DJ, Ross MD, et al. Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans. *Science (80-).* 2010;329(5993):841–845. doi:10.1126/science.1193032
34. Reeves-Daniel AM, DePalma JA, Bleyer AJ, et al. The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant.* 2011;11(5):1025–1030. doi:10.1111/j.1600-6143.2011.03513.x [PubMed: 21486385]
35. Freedman BI, Julian BA, Pastan SO, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant.* 2015;15(6):1615–1622. doi:10.1111/ajt.13223 [PubMed: 25809272]
36. Freedman BI, Pastan SO, Israni AK, et al. APOL1 Genotype and Kidney Transplantation Outcomes From Deceased African American Donors. *Transplantation.* 2016;100(1):194–202. doi:10.1097/TP.0000000000000969 [PubMed: 26566060]
37. Lee BT, Kumar V, Williams TA, et al. The APOL1 Genotype of African American Kidney Transplant Recipients Does Not Impact 5-Year Allograft Survival. *Am J Transplant.* 2012;12(7):1924–1928. doi:10.1111/j.1600-6143.2012.04033.x [PubMed: 22487534]
38. Kozlitina J, Zhou H, Brown PN, et al. Plasma Levels of Risk-Variant APOL1 Do Not Associate with Renal Disease in a Population-Based Cohort. *J Am Soc Nephrol.* 2016;27(10):3204–3219. doi:10.1681/ASN.2015101121 [PubMed: 27005919]
39. Callender CO, Cherikh WS, Miles PV, et al. Blacks as Donors for Transplantation: Suboptimal Outcomes Overcome by Transplantation Into Other Minorities. *Transplant Proc.* 2008;40(4):995–1000. doi:10.1016/j.transproceed.2008.03.063 [PubMed: 18555098]
40. Doshi MD, Ortigosa-Goggins M, Garg AX, et al. APOL1 Genotype and Renal Function of Black Living Donors. *J Am Soc Nephrol.* 2018;29(4):1309–1316. doi:10.1681/ASN.2017060658 [PubMed: 29339549]

41. Neugut YD, Mohan S, Gharavi AG, Kiryluk K. Cases in Precision Medicine: APOL1 and Genetic Testing in the Evaluation of Chronic Kidney Disease and Potential Transplant. *Ann Intern Med.* 10 2019. doi:10.7326/M19-1389
42. Freedman BI, Moxey-Mims M. The APOL1 Long-Term Kidney Transplantation Outcomes Network-APOLLO. *Clin J Am Soc Nephrol.* 2018;13(6):940–942. doi:10.2215/CJN.01510218 [PubMed: 29703792]
43. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet.* 2018;50(9):1219–1224. doi:10.1038/s41588-018-0183-z [PubMed: 30104762]
44. Khera AV, Chaffin M, Wade KH, et al. Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. *Cell.* 2019;177(3):587–596.e9. doi:10.1016/j.cell.2019.03.028 [PubMed: 31002795]
45. Liu L, Kiryluk K. Genome-wide polygenic risk predictors for kidney disease. *Nat Rev Nephrol.* 2018;14(12):723–724. doi:10.1038/s41581-018-0067-6 [PubMed: 30279535]
- 46 *. Stapleton CP, Heinzel A, Guan W, et al. The impact of donor and recipient common clinical and genetic variation on estimated glomerular filtration rate in a European renal transplant population. *Am J Transplant.* 2019;19(8):ajt.15326. doi:10.1111/ajt.15326 This is the first study that used donor's and recipient's polygenic risk score (PRS) for eGFR to predict allograft function.
47. Pattaro C, Teumer A, Gorski M, et al. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun.* 2016;7(1):10023. doi:10.1038/ncomms10023 [PubMed: 26831199]
48. Vilhjálmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet.* 2015;97(4):576–592. doi:10.1016/j.ajhg.2015.09.001 [PubMed: 26430803]
49. Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet.* 2019;51(6):957–972. doi:10.1038/s41588-019-0407-x [PubMed: 31152163]
50. O'Brien RP, Phelan PJ, Conroy J, et al. A genome-wide association study of recipient genotype and medium-term kidney allograft function. *Clin Transplant.* 2013;27(3):379–387. doi:10.1111/ctr.12093 [PubMed: 23432519]
51. Pihlstrøm HK, Mjøen G, Mucha S, et al. Single Nucleotide Polymorphisms and Long-Term Clinical Outcome in Renal Transplant Patients: A Validation Study. *Am J Transplant.* 2017;17(2):528–533. doi:10.1111/ajt.13995 [PubMed: 27483393]
52. Ghisda L, Baron C, Lebranchu Y, et al. Genome-Wide Association Study of Acute Renal Graft Rejection. *Am J Transplant.* 2017;17(1):201–209. doi:10.1111/ajt.13912 [PubMed: 27272414]
53. Hernandez-Fuentes M, Stapleton CP, Cavalleri GL, et al. The genetic determinants of renal allograft rejection. *Am J Transplant.* 2018;18(8):2100–2101. doi:10.1111/ajt.14909 [PubMed: 29719114]
54. Dai Y, Hebert MF, Isoherranen N, et al. EFFECT OF CYP3A5 POLYMORPHISM ON TACROLIMUS METABOLIC CLEARANCE IN VITRO. *Drug Metab Dispos.* 2006;34(5):836–847. doi:10.1124/dmd.105.008680 [PubMed: 16501005]
55. Jacobson PA, Oetting WS, Brearley AM, et al. Novel Polymorphisms Associated With Tacrolimus Trough Concentrations: Results From a Multicenter Kidney Transplant Consortium. *Transplantation.* 2011;91(3):300–308. doi:10.1097/TP.0b013e318200e991 [PubMed: 21206424]
56. Oetting WS, Schladt DP, Guan W, et al. Genomewide Association Study of Tacrolimus Concentrations in African American Kidney Transplant Recipients Identifies Multiple CYP3A5 Alleles. *Am J Transplant.* 2016;16(2):574–582. doi:10.1111/ajt.13495 [PubMed: 26485092]
57. Oetting WS, Wu B, Schladt DP, et al. Genome-wide association study identifies the common variants in CYP3A4 and CYP3A5 responsible for variation in tacrolimus trough concentration in Caucasian kidney transplant recipients. *Nat Publ Gr.* 2017;18:501–505. doi:10.1038/tpj.2017.49
58. Oetting WS, Wu B, Schladt DP, et al. Genetic Variants Associated With Immunosuppressant Pharmacokinetics and Adverse Effects in the DeKAF Genomics Genome-wide Association

Studies. Transplantation. 2019;103(6):1131–1139. doi:10.1097/TP.0000000000002625 [PubMed: 30801552]

59. Tsai Y-C, Chen H-M, Hsiao S-M, et al. Association of physical activity with cardiovascular and renal outcomes and quality of life in chronic kidney disease. Aguilera AI, ed. PLoS One. 2017;12(8):e0183642. doi:10.1371/journal.pone.0183642 [PubMed: 28832653]
60. Gillis KA, Patel RK, Jardine AG. Cardiovascular complications after transplantation: Treatment options in solid organ recipients. Transplant Rev. 2014;28(2):47–55. doi:10.1016/j.trre.2013.12.001
61. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2):178–185. <http://www.ncbi.nlm.nih.gov/pubmed/12603213>. Accessed September 2, 2019. [PubMed: 12603213]
62. Cole EH, Johnston O, Rose CL, Gill JS. Impact of Acute Rejection and New-Onset Diabetes on Long-Term Transplant Graft and Patient Survival. Clin J Am Soc Nephrol. 2008;3(3):814–821. doi:10.2215/CJN.04681107 [PubMed: 18322046]
63. McCaughan JA, McKnight AJ, Maxwell AP. Genetics of new-onset diabetes after transplantation. J Am Soc Nephrol. 2014;25(5):1037–1049. doi:10.1681/ASN.2013040383 [PubMed: 24309190]
64. Sanders ML, Karnes JH, Denny JC, Roden DM, Ikizler TA, Birdwell KA. Clinical and Genetic Factors Associated With Cutaneous Squamous Cell Carcinoma in Kidney and Heart Transplant Recipients. Transplant Direct. 2015;1(4):1–7. doi:10.1097/TXD.0000000000000521
- 65 *. Pihlstrøm HK, Mjøen G, Mucha S, et al. Genetic markers associated with long-term cardiovascular outcome in kidney transplant recipients. Am J Transplant. 2019;19(5):1444–1451. doi:10.1111/ajt.15191 [PubMed: 30457209] This is the first study that applied genetic risk score for cardiovascular disease to the transplant setting, demonstrating its utility in cardiovascular risk stratification.
- 66 *. Stapleton CP, Birdwell KA, McKnight AJ, et al. Polygenic risk score as a determinant of risk of non-melanoma skin cancer in a European-descent renal transplant cohort. Am J Transplant. 2019;19(3):801–810. doi:10.1111/ajt.15057 [PubMed: 30085400] This is the first study that demonstrated that polygenic risk score (PRS) for skin cancer is predictive of the disease in the renal transplant setting.

Key points

- The “**missense hypothesis**” refers to a donor-recipient genetic mismatch in non-synonymous (missense) variants, leading to peptide sequence incompatibilities in allograft-expressed proteins. This situation may cause allosensitization and rejection.
- The “**genomic collision**” refers to a genetic mismatch where homozygous gene-disrupting (loss-of-function) variants are present in the recipient but not in the donor, leading to allorecognition of the intact gene product when expressed in the allograft. This situation may represent an underrecognized cause of rejections.
- The **APOL1 risk genotypes** are present in 15% of African Americans and have been associated with shortened allograft survival when present in the donor. However, the donation risk for living kidney donors with the risk genotype are presently uncertain motivating the ongoing APOLLO study.
- Newer formulations of genome-wide **polygenic risk scores** for kidney function and CKD may provide useful tools for prediction of allograft function and donor risks, but their clinical utility will require rigorous testing in diverse ancestries and transplant settings.
- The role of polygenic risk models in predicting common transplant comorbidities, such as cardiovascular disease, diabetes, infections, or cancer need to be addressed by additional studies across diverse ancestries and different types of transplants.
- Most of the genetic variance in tacrolimus levels is explained by the known **loss-of-function variants in CYP3A5**. Pharmacogenomic testing for these variants may provide a useful tool for personalizing tacrolimus dosing and reducing the related side effects.
- There is a clear need for larger efforts to enable high-quality donor, recipient, and donor-recipient interaction GWAS to uncover precise genetic mechanisms underlying rejection and allograft survival.

Genetics of Transplant Outcomes

Figure 1. Genetics of Transplantation Outcomes.

GWAS designs can be broadly divided into those investigating donor's genetic background, recipient's genetic background, and donor-recipient genetic compatibility; APOL1 = Apolipoprotein L1; LOF = loss-of-function.