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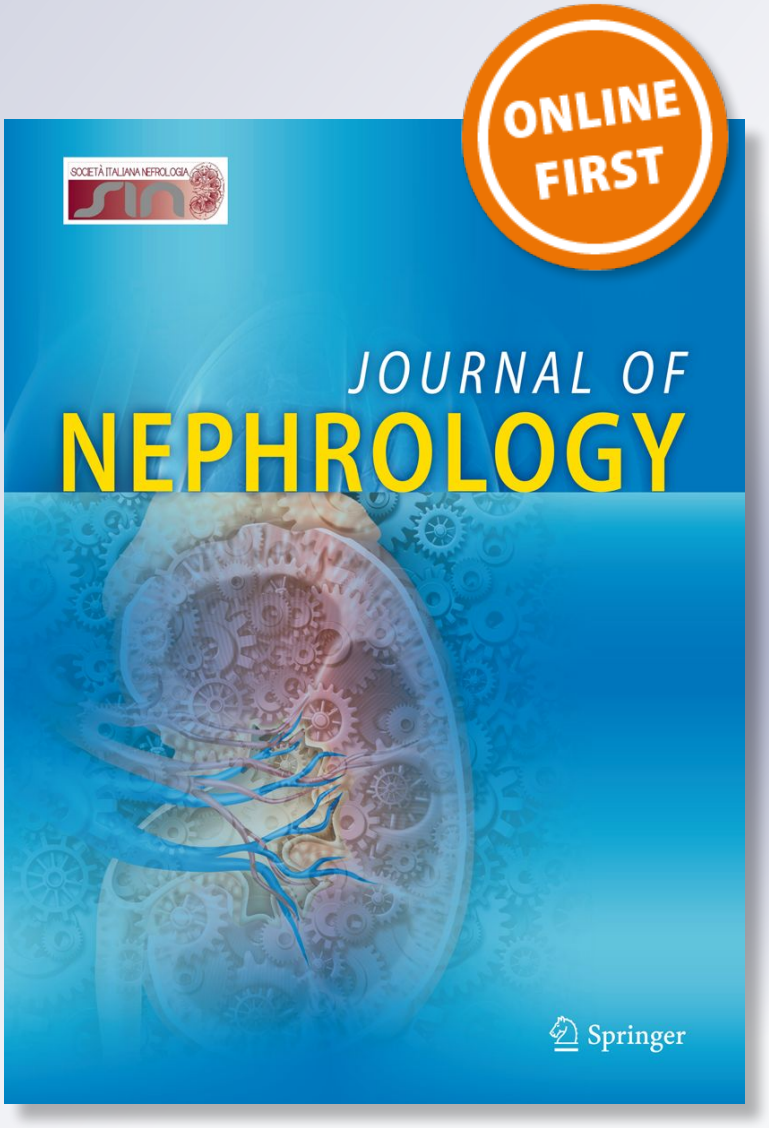

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REVIEW

Genetic determinants of renal transplant outcome: where do we stand?

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Abstract Kidney transplantation has become the preferred method of renal replacement. However, the rate of long term allograft survival has not changed over the last decade. Donor and recipient genetic interplay influences kidney transplant outcome but our knowledge of these complex interactions is limited. Until recently, investigations have been limited to small candidate gene studies, usually restricted to allograft recipients. Genome-wide association studies have been slow to emerge in transplantation but the first has recently been reported and will be reviewed here. Much larger studies involving donor and recipients pairs are ongoing. We are now entering the era of epigenetics and whole genome sequencing which will hopefully provide a more in-depth knowledge of the genetic influences on renal transplant outcome. This may lead to a more accurate assessment of post-transplant risk, potentially allowing for the development of risk predication models leading to a more personalized approach to kidney transplant care. In this article, we examine the current and emerging literature in the field and discuss the limitations of current studies and technologies.

Keywords Acute rejection · Genetics · GWAS · Kidney transplantation · Outcome · SNP

P. J. Phelan (✉)
Duke University Medical Center, Durham, NC, USA
e-mail: paulphel@gmail.com

P. J. Conlon
Department of Nephrology, Beaumont Hospital, Dublin, Ireland

M. A. Sparks
Department of Medicine, Division of Nephrology,
Duke University and Durham VA Medical Centers,
Durham, NC, USA

Background

Interactions between the donor and recipient genome have long been known to influence renal allograft survival [1, 2]. This effect has been apparent since the first successful transplant of a kidney between two genetically identical individuals and the subsequent observation of the excellent outcomes in human leukocyte antigen (HLA)-identical siblings. Our current pre-transplant genetic testing has not changed for several decades and consists of donor/recipient matching at the HLA loci A, B and DR, with some units also matching at DQ and DP in recent years. While important, this approach is simplistic and does not accurately identify the risk of immunological events post-transplant. Moreover, the effect of HLA-matching regarding transplant survival is at best modest [3], particularly in deceased donors, and may be declining in the current era of improved immunosuppression [4, 5]. Despite this possible blunting of the HLA effect, allograft half-life remains suboptimal and lags well behind improvements in short-term outcome. Recent evidence from several groups, such as the Collaborative Transplant Study (CTS) and the Deterioration in Kidney Allograft Function (DeKAF) Study, suggest that immunological injury may be paramount and that late allograft loss may be predominantly due to chronic antibody mediated rejection [6, 7]. This is despite low rates of acute rejection in the current era. We will review the current literature of the genetic determinants of allograft outcome, the limitations of studies performed so far and future directions.

Pathogenesis

Allograft survival rates differ between populations, with evidence that European populations do better than US

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patients, and that US whites have better graft survival than US African Americans (AAs; see donor variants section) [8]. The current 5-year graft survival in the US for primary deceased donor kidney transplants is only 72 % [9]. This has only marginally improved over the past two decades despite marked improvements in 1-year graft survival with latest generation immunosuppression [10]. Late graft failure therefore remains the most significant outcome measure post-transplant and is an area in which we have made little progress despite improvements in early loss. Excluding death with a functioning graft, the most common cause of allograft failure after the first year is an incompletely understood clinic-pathological entity previously termed chronic allograft nephropathy. Other names such as chronic renal allograft dysfunction, transplant glomerulopathy and chronic allograft injury may be synonymous, and are a reflection of how imprecise our current knowledge of the mechanism of injury is [11, 12]. In this regard, it is clear that both immunological and non-immunological injury can co-exist. Furthermore, interstitial fibrosis and tubular atrophy (IF/TA) has gained popularity as a pathologically descriptive term in cases of chronic allograft injury. Similarly to many other kidney diseases, the degree of IF/TA correlates with severity and likelihood of progression to end-stage renal disease (ESRD) in patients who have received a kidney transplant [13]. As mentioned above, emerging evidence from several groups, including the DeKAF study amongst others [14], suggests that chronic allograft nephropathy may be primarily due to immunological injury, specifically chronic antibody-mediated rejection [7]. The genetic associations with chronic allograft injury and allograft loss are poorly understood although groups such as DeKAF are actively investigating this area [15–17]. The Mayo Clinic group has investigated the causes of allograft loss, determined by reviewing clinical and histological data, in 1,317 conventional kidney recipients [18]. Over the mean follow up of 50 months, 25 % of allografts were lost. Death with a functioning graft and primary non-function accounted for >50 % of causes of these graft failures. Of the remaining cases, the histological diagnoses were glomerular in nature (recurrent disease and transplant glomerulopathy, 37 %), IF/TA (31 %), medical or surgical conditions (16 %), acute rejection (AR, 12 %) and the remainder unclassifiable (<5 %). Contrary to recent thinking, a specific etiology in cases of IF/TA was identified in 81 % of cases. Calcineurin inhibitor (CNI) toxicity alone was only implicated in <1 % of cases. This study, supporting emerging evidence from DeKAF, illustrates that late renal allograft loss may be predominantly due to antibody-mediated rejection rather than CNI toxicity or other causes.

Genetics clearly plays a role in outcome of renal transplantation and this is supported by the finding of extensive and unexplained variation in rates of AR and allograft function between individuals and between

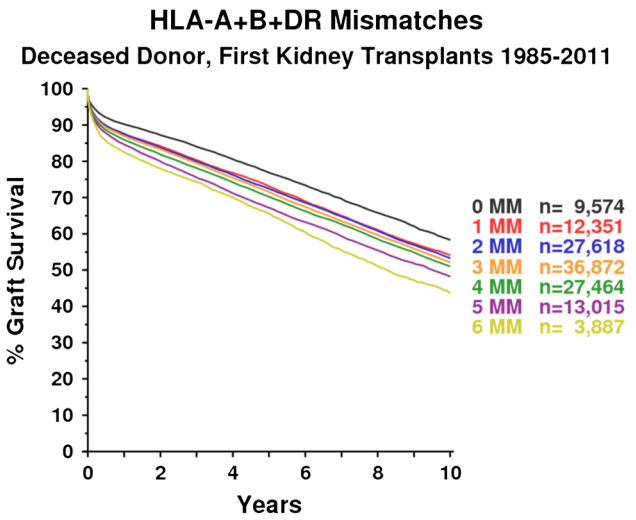

Fig. 1 Renal allograft outcome for first time transplants as per degree of HLA mismatch (www.ctstransplant.org on 7/10/13; used with permission from Prof Gerhard Opeltz). *CTS* Collaborative transplant study

recipient ethnic groups [19, 20]. Moreover, it is well established that identical twin transplants have a far superior allograft half-life (often without immunosuppression), with deceased donor transplants having the shortest graft survival and non-twin related transplants falling in-between these groups [1]. The antigen matching which is routinely performed is between the HLA-A, HLA-B and HLA-DR loci. The degree of HLA mismatching correlates with transplant survival. There is a step-wise decrease in allograft survival with increasing HLA mismatching (from zero to 6 mismatches) across the HLA-A, B and DR loci (see Fig. 1). HLA-DR mismatches appear to be the most immunogenic and correlate with poor long-term survival [21, 22]. Each HLA antigen appears to exert its effect at variable post-transplant times, with the maximal effect of DR and B mismatches occurring within the first 6 months and 2 years post-transplantation, respectively [23]. Successful allograft outcome is not guaranteed with good HLA matching, and as mentioned, may be diminishing with modern immunosuppression [5]. Therefore, the HLA system does not explain all of the likely genetic variance with transplant outcome.

Candidate gene studies

Over the past number of years, a small number of investigators have begun to study the impact candidate genes outside of the HLA system on kidney allograft outcome. These studies have identified genetic variation in multiple cytokines, chemokine receptors as well as allotypes of complement component C3 that each have been shown to

Table 1 List of donor and recipient candidate gene SNPs associated with outcome after renal transplantation

Gene	Association	Study size	Replication	Population	References
Recipient variants					
ABCB1	DGF/LTGF	172	N	Netherlands	[30]
ACE	AR	206	N	China	[58]
ATR 1	AR	206	N	China	[58]
ATR 1	Decline in eGFR	445	N	US	[59]
Beta 3 integrin	AR	424	N	US (mixed)	[60]
C3[a]	LTGF	513	N	UK	[25]
C5[a]	eGFR	191	N	Korea	[61]
CCL5	AR (recurrent)	261	N	Germany	[62]
CCR2	AR	167, 163	N	Korea, US	[63, 64]
CCR5	AR	163	N	US	[64]
CTLA4	AR	167	N	US	[65]
Factor V Leiden	AR, DGF, LTGF	394	N	Caucasian	[66]
Fc gamma receptor IIA	AR	99	N	Australia	[67]
GPIIIa	AR, LTGF	119	N	Spanish	[68]
IL-1	AR, DGF	136	N	India	[69]
IL-2	AR, LTGF	63	N	Brazil	[70]
IL-3	AR	330	N	Korea	[71]
IL-6	LTGF	197	N	Poland	[72]
IL-8	AR	296	N	India	[73]
IL-10	AR	88	N	UK	[74]
IL-18	DGF	124	N	Czech	[75]
IFN-gamma	AR, LTGF	88	N	UK	[74]
ICAM-1	AR	42	N	Iran	[76]
ICOS	DGF	678	N	Finland	[77]
IMPDH1	AR	191	N	US (mixed)	[78]
IMPDH2	AR	237	N	Spain	[79]
MCP-1	AR	167	N	Korea	[59]
STAT4	AR	453	N	China	[80]
TGF-B1	AR (recurrent)	164	N	Korea	[81]
TLR4	AR	238	N	France	[82]
TNF-alpha	AR (recurrent)	164	N	Korea	[81]
VDR (FokI)	LTGF	379	N	Ireland	[83]
VEGF	LTGF	555	N	Caucasian	[84]
Donor variants					
ABCB1	LTGF	881[b]	Y	Caucasian	[30, 40]
APOL1	LTGF	136	N	African American	[37]
Caveolin 1	LTGF	785[b]	Y	Caucasian	[41]
C3[a]	LTGF	513	N	UK	[25]
C5[a]	eGFR	191	N	Korea	[61]
eNOS	AR, LTGF	125	N	Poland	[85]
PAI 1	LTGF	125	N	Poland	[85]

AR acute rejection, *ATR 1* angiotensin type 1 receptor, *CAN* chronic allograft nephropathy, *CTLA* cytotoxic T-lymphocyte antigen, *DGF* delayed graft function, *eNOS* endothelial nitric oxide synthase, *GPIIIa* platelet glycoprotein III a, *ICOS* inducible T-cell co-stimulator, *LTGF* long term graft function, *PAI* plasminogen activator inhibitor, *VDR* vitamin D receptor (FokI polymorphism), *VEGF* vascular endothelial growth factor

[a] Donor/recipient study

[b] Size of discovery cohort. Study size = number of recipients in each study (including donor studies)

correlate with clinical outcome in different studies [24, 25]. The endpoint most frequently used has been early AR, although, with the excellent prognosis for early AR in the current era, we feel that allograft failure is a much more clinically relevant outcome. It is beyond the scope of this article to list the variants associated with AR in previous candidate gene studies but an excellent review of this subject was performed by Rumyantzev-Goldfarb et al. [26]. Most candidate gene studies performed so far have been small studies in diverse populations, not corrected for multiple testing (where >1 variant was studied) and not subject to replication in an independent cohort. See Table 1 for a list of

candidate gene studies -both donor and recipient—which have been associated with renal allograft outcome.

Drug-metabolizing genes have been a particular area of focus in the kidney transplant literature, especially the cytochrome P-450 system and the *ABCB1* gene (also called MDR-1 or multi-drug resistance gene; see Donor variant section). CNIs, the cornerstone of transplant immunosuppression, are metabolized by the cytochrome P450 (CYP) 3A4 and 3A5 enzymes. The major efflux pump which transports CNIs is P-glycoprotein, coded for by the *ABCB1* gene. There are multiple known polymorphisms with functional effects in these genes. Associations have been described between *CYP3A* and *ABCB1* variants and CNI drug levels [27, 28], delayed graft function (DGF) and allograft dysfunction [29] post kidney transplantation. Other studies show no impact between polymorphisms in these drug metabolizing genes and acute rejection [30, 31]. The CYP3A4*22 allele has been linked to reduced hepatic expression and activity of CYP3A4. Li et al. [28] studied 172 European first-time kidney transplant patients receiving cyclosporine and levels were monitored on days 3 and months 1, 3, 6, and 12 post-transplantation. In a multifactorial model, the CYP3A4*22 allele was significantly associated with a higher risk of DGF (odds ratio = 6.34, $p = 0.015$). The study also demonstrated that the creatinine clearance was 20 % lower in CYP3A4*22 allele carriers ($p = 0.002$). There was no association between the CYP3A4*22 variant and the development of AR. The authors hypothesize that this higher risk of DGF with the CYP3A4*22 allelic variant is because of a reduced CYP3A4 enzymatic activity, which has been previously demonstrated. The potential influences of drug metabolizing gene variants and allograft outcomes need to be investigated further in large patient consortiums. This work is ongoing in European patient cohorts and has the potential to help individualize CNI dosing post-transplant.

The DeKAF group performed an attempted validation of several candidate gene single nucleotide polymorphisms (SNPs; variation at a single nucleotide) for AR in kidney transplantation [32]. In this report, the authors attempted to replicate 23 previously published candidate gene studies in AR of renal allografts. Patients were mostly kidney-only recipients (60 % living donor transplants), transplanted across 5 US centers between 2005 and 2008. Patients were predominantly white (76.2 %), male (62.1 %), and maintained on CNI-based immunosuppression (>97 %). Most studies examined multiple SNPs but the results were not adjusted for multiple testing. Only the SNP located in Factor V had a strongly significant result in this repeat study, with a variant in *IMPDH2* gene achieving marginal significance. This emphasizes the caution we must take when judging results from candidate gene studies.

Donor variants and transplant outcome

The unique nature of transplantation, with the interaction of donor and recipient genetic material, opens up huge potential to study the prospective donor influences on allograft outcome. There are far less data available on the relationship between donor and recipient SNPs and subsequent transplant outcome. A number of clinical studies have examined the effect of paired donor kidneys transplanted into different recipients to assess concordance in transplant outcome between pairs of recipients receiving genetically identical kidneys. One study demonstrated no difference in renal transplant outcome between the recipients of left and right-sided kidneys from an identical deceased donor [33]. Two other studies reported a significant degree of correlation within pairs of kidneys transplanted from the same donor for delayed graft function (DGF) [34, 35] and for serum creatinine post-transplant [34]. The larger of these studies [35] employed United States Renal Data System (USRDS) data of almost 12,000 common-donor transplant pairs and demonstrated a recipient was twice as likely to develop DGF when the recipient of the contralateral kidney developed DGF. These clinical studies suggest that unmeasured donor characteristics contribute to outcome after transplantation. A number of donor-recipient studies have recently been performed which should be commended for examining the hard end-point of allograft survival, rather than just AR.

Two studies looking at C3 polymorphisms in donors and recipients have yielded conflicting results with respect to long-term transplant outcome. The variants studied were named C3F (fast) and C3S (slow) on the basis of their electrophoretic motility. Brown et al. [25] suggested that in C3S/S recipients, receipt of a C3F/F or C3F/S donor kidney, rather than a C3S/S donor kidney, is associated with a significantly better long term outcome ($n = 513$). However, a subsequent larger study on 1,147 donor and recipient pairs demonstrated that transplantation of C3F/S or C3F/F kidneys to C3S/S recipients is not advantageous with regard to transplant survival or cumulative rates of AR and allograft dysfunction [36].

Variants in the apolipoprotein L1 gene (APOL1), termed G1 and G2, are strongly associated with kidney disease in AAs. These variants are common in people of African ancestry and are generally not seen in European populations. The mutations became prevalent in African populations due to positive selection resulting from the survival advantage provided by APOL1 from *Trypanosoma brucei rhodesiense* infection. These variants are found in 10–12 % of AAs and the risk of allograft failure from donors harboring these polymorphisms was significantly higher in a study of 106 AA donors (adjusted

hazards ratio, HR 3.84) [37]. Interestingly, recipient APOL1 genotypes do not appear to impact allograft outcomes in a study of 119 AA donors [38]. This donor risk finding needs to be replicated and would have implications for kidney donation from AAs. There is also the separate issue of living donation from a patient with these alleles regarding their future risk of kidney disease. It would seem important to assess any increased risk of ESRD from an AA who possesses APOL1 risk variants and subsequently donates a kidney.

ABCB1 donor polymorphisms have been associated in a French kidney transplant population with worse allograft survival [39]. A more recent and larger study suggested an association between genetic variation in donor *ABCB1*, known to influence CNI metabolism, and allograft failure [40]. The discovery cohort was from the UK ($n = 811$) and replication was performed in a group from Belfast ($n = 675$) and the CTS cohort ($n = 2{,}985$). The study investigated the relationship of both donor and recipient *ABCB1* genotype, specifically the C3435T polymorphism also examined in the above French study, with kidney allograft survival. Most patients across the 3 cohorts were treated with cyclosporine rather than tacrolimus, including all the discovery patients. The rs1045642 SNP within the *ABCB1* gene was significantly associated with an increased risk for long-term allograft failure (HR 1.69; $p = 0.003$). The effect of rs1045642 on transplant loss was replicated in the Belfast population (HR 1.68; $p = 0.002$). Overall in the CTS cohort no association was demonstrated between the donor ABCB1 genotype and death-censored allograft survival. However, in the subgroup of 452 tacrolimus treated patients an association between donor genotype and death-censored allograft survival was seen (HR 1.84; $p = 0.006$).

Another validated study was performed concerning polymorphisms in the gene encoding caveolin-1. Caveolae are plasma membrane proteins involved in G protein signaling and found to be inhibitors of tissue fibrosis. The discovery cohort consisted of 785 kidney transplant donors and recipients from the UK and the replication cohort had 697 pairs from Belfast [41]. The SNP rs4730751 was significantly associated with allograft failure in both populations. A follow up study of a caveolin-2 variant did not support an association with kidney transplant survival, due to inability to replicate the effects demonstrated in the discovery cohort [42]. This was due to the variant in the original cohort not being found in the replication cohort. Re-sequencing of the gene found that the 'SNP' was due to misalignment of bases; it re-enforces the importance of replication using a different technology and demonstrates the potential for SNPs to be mistakenly identified and reported in genetic studies.

Recent advances

The advent of genome-wide association studies

The human genome consists of approximately 3 billion nucleotides of DNA sequence, most of which have now been identified. Areas of variance at a single nucleotide have allowed for the creation of a map of SNPs across the genome at intervals of about one per 300 base pairs of DNA [43]. The International HapMap Project undertook this work and has made the results freely available for other researchers (hapmap.ncbi.nlm.nih.gov). The minor allele frequency (MAF) refers to the percentage of all alleles at a given locus in a population represented by a particular allele. The mechanisms of human inheritance are such that SNPs in close physical proximity (usually <50 kb apart) are more likely to be inherited together. This phenomenon is termed linkage disequilibrium (LD) and allows for one SNP in such a group (haplotype) to serve as a surrogate marker for the presence of other SNPs in that haplotype. This removes a lot of redundancy in the genome, obviating the need for individual genotyping of every SNP. This is the principle behind genome-wide association studies (GWAS). The first GWAS in renal transplantation was recently reported [44]. It utilized a small discovery cohort from Ireland involving 326 first-time, deceased-donor, kidney-only transplant recipients who received CNI based immunosuppression. To assess long-term allograft function, analysis of the serum creatinine at 5 years post-transplant was examined and was available in 263 patients. After correcting for multiple testing (necessary in GWAS due to the very large number of tests performed), 2 SNPs demonstrated genome-wide levels of significance. The first SNP was on chromosome 18 (rs6565887; $p = 4.048 \times 10^{-8}$) and is located in an intergenic region of the T cell receptor alpha locus, which is a biologically interesting area as the T cell receptor confers antigen specificity of immune responses. The second SNP was on chromosome 14 (rs3811321; $p = 7.631 \times 10^{-8}$) and is located in a non-coding intronic variant of ZNF516 (zinc finger protein 516). Zinc finger proteins bind DNA and regulate gene transcription. There are currently no known human phenotypes associated with the ZNF516 gene or specifically with the rs6565887 variant. After fitting a linear model between 5-year creatinine and the sample genotypes, the two SNPs explained up to 11.29 % (chromosome 14 locus) and 8.8 % (chromosome 18 locus) of 5-year creatinine variance. Together they explained up to 17.4 % of trait variance. The effect sizes estimated here are almost certainly overestimated as they have been calculated in the cohort in whom the discovery was made (so-called 'winners curse'). In order to assess the results as possible indicators of allograft failure, a time-to-event transplant

survival analysis was undertaken for rs3811321 and rs6565887 from the entire cohort of 326 patients. Both variants were predictors of long-term allograft function ($p = 0.004$, 70 % versus 30 % survival at 10 years). These results seem encouraging given their effect size in a limited-sized GWAS and the biologically plausible variant in the T cell receptor alpha locus. These findings warrant replication in an independent cohort.

International consortia

A number of groups are actively investigating transplant injury and outcome using the latest functional genomics and molecular techniques. The UK and Ireland Renal Transplant Consortium (UKIRTC) was created in response to a call from the Wellcome Trust Case Control Consortium 3 programme and represents every kidney transplant center in the UK and Ireland (www.ukirtc.org). The UKIRTC study involves a planned primary genotyping scan of 2,500 Caucasian renal transplant pairs. Replication for loci of potential interest is planned in up to 7,000 donor recipient pairs. The study has enrolled patients and initial genotyping is complete. The data this study generates will hopefully add greatly to our understanding of the genetic influences on early and late allograft dysfunction. A primary outcome in the UKIRTC GWAS is allograft survival employing a time-to-event model. Other groups include Scripps Center for Organ and Cell Transplantation, Mount Sinai's Recanati/Miller Transplantation Institute and the DeKAF study group who will study genetic variants linked to immunological responses to kidney allografts.

GWAS challenges

GWAS have revolutionized the search for genetic influences on complex diseases. The common disease/common variant hypothesis presumes that genetic influences on susceptibility to common diseases are attributable to a limited number of variants (MAF >1–5 % of the population). However, unlike single gene disorders, complex diseases, which would include renal transplant failure, are likely caused by the interplay of a multitude of genetic and environmental factors. Each genetic variant is usually found to have a relatively small independent effect on the development of the trait and few, if any, may be obligatory for the disease to occur.

LD is crucial to the principal of GWAS as discussed above. However, only a small number of SNPs that are associated with traits in GWAS are located in or occur in tight LD with protein-coding regions of genes (exons). Furthermore, this occurs despite the fact that SNPs in exons are over-represented on genotyping arrays [45]. Hindorff et al. [46] examined 151 published GWAS and demonstrated that approximately 43 % of trait-associated SNPs fall in intergenic regions of the genome, with another 45 % located in non-coding introns. These SNPs are unlikely themselves to be causative variants but may be markers for a trait due to strong LD with the functional polymorphism. However, SNPs falling in intergenic regions, far from any coding region (so-called 'gene deserts') may still be real effects despite initial concerns that they were spurious associations [47, 48].

Rare variants are not well covered by current GWAS techniques. SNPs with a MAF <5 % have poor coverage and routine cleaning protocols exclude SNPs with very low allele frequencies. The 1,000 Genomes Project is attempting to address this problem by compiling a dataset of SNPs with MAF >1 and <5 % for potential inclusion in fine-mapping efforts and expanded genome-wide association arrays (http://www.1000genomes.org). Fine mapping involves typing all of the known SNPs in a haplotype block represented by the identified tag SNPs to determine whether any of these SNPs have a stronger association than the tag SNP identified in the genome-wide scan. It is quite possible that rare variants account for some of the additional risk that is not explained by current GWAS techniques. Larger studies that identify more variants are likely to identify SNPs with even smaller effect sizes. Apart from SNPs, other genetic variants need to be studied such as copy number variation (CNV; deletions and duplications comprising approximately 10 % of the genome), translocations and inversions. There is evidence that CNV might explain more genetic risk than was previously thought, however, CNV analysis will pose increased bioinformatic challenges [49].

Future directions

As described above, each single genetic variant or SNP may individually contribute a very small amount to the overall trait risk, but grouped together multiple SNPs may have a strong effect. This is the concept behind genetic risk prediction modeling. Employing very large patient cohorts, it may be possible to explain a sizable proportion of risk of acute rejection or allograft failure based on a large panel of SNPs. These risk models could potentially be performed pre-transplant, in both recipient and donor, to help determine post-transplant risk or even help in the matching process. Initial efforts will need to involve the creation of worldwide collaborations incorporating all renal transplant genomic studies due to the need for large patient numbers to make meaningful observations. These models are speculative at present in transplantation but the technology exists to perform these studies. Cost and utility will be major factors.

New technologies such as whole exome and whole genome sequencing are becoming more available due to diminishing costs. These techniques have the potential to reveal important findings in the field of kidney transplantation. However, these studies remain to be performed. The challenge will then be for the bioinformatics technology to keep pace with the huge volumes of new data gathered.

Epigenetics

The influence of epigenetic mechanisms on disease development is a current hot topic in genetic research. It refers to modifications of gene expression at the level of gene transcription and translation without alterations to the gene sequence. These processes are modifiable by the cellular environment and potentially inheritable [50]. Epigenetic mechanisms encompass changes to DNA or chromatin via DNA methylation, histone modifications and RNA interference (often involving micro-RNA expression). Through these effects on chromatin structure, epigenetic changes can modulate transcriptional repression, X-chromosome inactivation and genomic imprinting. The study of epigenetics in renal transplantation is in its infancy but emerging data show promise. Aberrant methylation of DNA has been reported to be related to polymorphisms of MTHFR which may influence skin cancer development post transplantation [51]. T regulatory cells (Tregs) play an important role in modulation of the immune system and immune recognition [52]. They restrict self-reactive T cells and have been shown to suppress allograft rejection and may influence allograft function post renal transplant [53]. Epigenetic regulation is critical to the function of Tregs. FOXP3 is a transcriptional factor expressed by Tregs and essential for their regulation. FOXP3 also appears to play a role in creating antigen-specific unresponsiveness that is sustained in the absence of chronic immunosuppression i.e., tolerance [54]. The expression of FOXP3 is governed by methylation/demethylation of Tregs [55]. Operational tolerance, i.e., allograft survival without the need for life-long immunosuppression, is an obvious goal for transplant physicians. An understanding of the epigenetic modifications of Tregs could conceivably pave the way for in vitro or in vivo manipulation of the immune system to achieve antigen-specific unresponsiveness [56]. It must be noted that epigenetic studies in renal transplantation may be challenging. As transcriptional mechanisms are likely to be tissue specific, studies may be limited to allograft biopsy samples although blood cell expression may also prove to be useful. An insightful review of epigenetics in transplantation has recently been published [57]. Newer exome chips include large coverage of microRNA regions and developing technologies and resources such as the NIH Epigenome Roadmap will facilitate more in-depth epigenome-wide association studies (EWAS).

Summary

Our current understanding of the genetic influences on renal transplant outcome, outside of the HLA system, is dominated by small, un-replicated candidate gene studies of unknown clinical relevance. There is a dearth of studies adopting hard endpoints such as allograft failure, with AR generally being the studied outcome. Large scale genotyping studies have been slow to appear in renal transplantation but GWAS data are beginning to emerge. These, along with studies with other modern techniques, will hopefully add to our understanding of the mechanisms of renal transplant dysfunction and enhance our current understanding of immunological risk. We currently lack the tools to accurately assess risk and prognosticate on an individual basis. Our ultimate aim with ongoing genetic studies in the field is to create clinically relevant tools, including risk predication models, so we may individualize transplant care based on genetic risk, which will improve outcomes.

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Conflict of interest None.

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