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Genetic polymorphisms in the immune response: A focus on kidney transplantation

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ABSTRACT

The modulation of the immune system following solid organ transplantation has made considerable progress with new immunosuppressive regimens and has considerably improved rejections rates. The improvement in long-term allograft survival is, however, modest. A complex network of cytokines, chemokines, adhesion, activation and co-stimulatory molecules are the frontline contributors to allograft rejection, which in turn determines the evolution of graft function and its long-term survival. Polymorphisms in these genes influence protein levels and presumably their signaling effects. In this review, we present a relevant panel of candidate genes related to the immune system in the context of solid organ transplantation; we discuss the most convincing reports of genetic associations with outcomes in renal transplantation and highlight the most promising loci among the vast body of literature.

1. Introduction

The success of solid organ transplantation depends on many donor or recipient characteristics including HLA mismatch, pre-formed antibodies, age and ethnicity, as well as on specific events linked to the surgical procedure (e.g., cold ischemia time, reperfusion injury). Careful use of immunosuppressants likewise has an impact, and while experience has led to the titration of these drugs to blood levels within thresholds to improve outcomes and avoid adverse effects, there remains unexplained variability in outcomes.

A large body of literature provides evidence that the efficacy and toxicity of immunosuppressive therapy might be mitigated by polymorphisms in important pharmacogenes related to their pharmacokinetics and, to a minor extent, pharmacodynamics. Only a few of the reported associations have translated into validated pharmacogenetic applications. Pharmacogenetics is defined as "the study of variations in DNA as related to drug response". Variations of interest are non-pathogenic and usually relatively common. Most studies in transplantation have focused on genetic variations that may change the relationship between the dose of the drug administered and its blood levels. The aim in this context was to obtain additional tools to better achieve or maintain levels in effective and non-toxic concentration targets. Genotyping of cytochrome P450 3A5 (CYP3A5; a key enzyme in tacrolimus hepatic clearance) is an example of routine application that was demonstrated to be beneficial to the refinement of tacrolimus first dose through a randomized multicentre trial [1]. However, the benefit in terms of clinical outcomes for the CYP3A5 specific example, and others, remains to be proven.

Pharmacogenetics of solid organ transplantation is indeed a very particular area: clinical outcomes are influenced by immunosuppressive therapy but additionally by the milieu of immune system players, including cytokines and their receptors, chemokines and their receptors, adhesion molecules, co-stimulatory molecules and innate immune system proteins which are the frontline contributors to rejection (or conversely to immune tolerance). This panel of cytokines provide a long list of less explored candidate genes in the search for polymorphisms that might be used to predict clinical outcomes, and thus tailor therapy based on risk.

Several excellent reviews exist on the topic of genetic polymorphisms in immune system genes and their impact on graft outcomes in solid organ transplantation [2–5]. The following review aims to highlight the loci that have been studied specifically in kidney transplantation related to outcomes of success (acute rejection, graft survival chronic allograft nephropathy, among others), and to present an update

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Table 1
Genes coding for the main proteins related to the immune response in the context of allograft transplantation.

Chromosome location	Gene	Name	Other names	Main function[a]
Genes related to initial T cell activation				
Co-stimulatory molecules				
2	*CD28*	CD28 molecule		Binds CD80/86 expressed by antigen-presenting cells to provide a co-stimulatory signal (T-cell activation, proliferation and a proinflammatory response)
3	*CD80*	CD80 molecule		
2	*CTLA4*	Cytotoxic T-lymphocyte-associated protein 4	CD152	Downregulates the immune system (acts as an "off" switch by stimulating the CD28 receptor on the T cell)
20	*CD40*	CD40 molecule	TNFRSF5	Mediates a broad variety of immune and inflammatory responses including T
X	*CD40LG*	CD40 ligand	CD154, CD40L	cell-dependent immunoglobulin class switching and memory B cell development
Regulatory molecules				
1	*PTPN22*	Protein tyrosine phosphatase, non receptor type 22		Negative regulator of TCR-signal
16	*CIITA*	Class II, major histocompatibility complex, transactivator		Master regulator of the HLA class II
Genes related to cytokines and receptors				
2	*IL1A*	Interleukin-1 alpha (IL-1α)		Produced by monocytes and macrophages, involved in inflammatory processes and hematopoiesis
2	*IL1B*	Interleukin-1 beta (IL-1β)	IL1F2, catabolin	Produced by activated macrophages (as a proprotein), involved in the inflammatory response (cell proliferation, differentiation, apoptosis)
2	*IL1R1*	Interleukin 1 receptor, type 1	CD121A, IL1RA	Receptor for interleukin-1 alpha, interleukin-1 beta, and interleukin-1 receptor antagonist
2	*IL1RN*	Interleukin-1 receptor antagonist (IL-1RA)		Inhibits the activities of interleukins 1, alpha and beta
4	*IL2*	Interleukin 2 (IL-2)	Lymphokine	Proliferation of T and B lymphocytes
22	*IL2RB*	Interleukin-2 receptor subunit beta (IL-2Rβ)	CD122	Component of intermediate and high affinity IL2-receptor, Involved in endocytosis and transduction of mitogenic signals from IL-2
5	*IL3*	Interleukin-3 (IL-3)		Potent growth promoting cytokine (mainly hematopoietic cells)
5	*IL4*	Interleukin 4 (IL-4)		Produced by activated T cells, immunoregulation (differentiation in TH2 cells)
16	*IL4R*	Interleukin 4 Receptor alpha	CD124	Binds IL-4 (to promote differentiation of Th2 cells) and IL-13 (to regulate IgE production)
7	*IL6*	Interleukin 6 (IL-6)	IFNB2	Functions in inflammation and the maturation of B cells also capable of inducing fever in people with autoimmune diseases or infections
1	*IL10*	Interleukin-10 (IL-10)		Produced primarily by monocytes, immunoregulation (differentiation in TH2 cells)
5	*IL12B*	Interleukin 12, subunit beta (IL12-B)		Expressed by activated macrophages, an essential inducer of Th1 cells development
6	*IL17A*	Interleukin 17 (IL-17)	CTLA8, IL-17A	T helper 17 (Th17) cells activation
11	*IL18*	Interleukin 18 (IL-18)	IGIF (IFNγ inducing factor)	Augments natural killer cell activity in spleen cells. Stimulates interferon gamma production in T-helper type I cells
4	*IL21*	Interleukin 21 (IL-21)		Role in both the innate and adaptive immune responses (differentiation, proliferation and activity of macrophages, natural killer cells, B cells and CTLs)
6	*TNFA*	Tumor necrosis factor (TNFα)	Cachexin, cachectin	Secreted by macrophages, proinflammatory cytokines (cell proliferation, differentiation, apoptosis)
6	*LTA*	Lymphotoxin alpha	TNFB (Tumor necrosis factor-beta)	Involved in inflammatory, immunostimulatory, and antiviral response, role in apoptosis, role in formation of secondary lymphoid organs during development
19	*TGFB1*	Transforming growth factor beta (TGF-β)		Regulates proliferation, differentiation, adhesion, migration, and other functions in many cell types
Genes related to the innate immune response				
4	*TLR2*	Toll-like receptor 2	CD282	Role in pathogen recognition and activation of innate immunity
9	*TLR4*	Toll-like receptor 4	CD284	
3	*TLR9*	Toll-like receptor 9	CD289	
19	*C3*	Complement component 3	C3b	Central role in the activation of complement system, antimicrobial activity
5	*CD14*	CD14 molecule		Expressed on monocytes/macrophages, cooperates with TLRs to mediate the innate immune response to bacterial lipopolysaccharide
Genes related to the effector phase of rejection (graft infiltration and injury)				
4	*CXCL8*	Chemokine (C–X–C motif) ligand 8	IL8	Chemoattractant for neutrophils, also a potent angiogenic factor
2	*CXCR1*	Chemokine (C–X–C motif) receptor 1	IL8RA, IL8R1, CD128, CD181	Interleukin 8 receptor (high affinity)
2	*CXCR2*	Chemokine (C–X–C motif) receptor 2	IL8RB, IL8R2, CD182	Interleukin 8 receptor (high affinity)
17	*CCL2*	Chemokine (C–C motif) ligand 2	MCP-1 (monocyte chemotactic protein 1)	Chemoattractant for monocytes and basophils
17	*CCL5*	Chemokine (C–C motif) ligand 5 (CCL5)	RANTES	Chemoattractant for blood monocytes, memory T helper cells and eosinophils
3	*CCR2*	C–C chemokine receptor type 2	CD192	CCL2 receptor
3	*CCR5*	C–C chemokine receptor type 5	CD195	CCL5 receptor
10	*CXCL12*	Chemokine (C–X–C motif) ligand 12	SDF1 (stromal cell-derived factor 1)	Ligand of chemokine (C–X–C motif) receptor 4, role in immune surveillance, inflammation response, tissue homeostasis, and tumor growth and metastasis
Other adhesion Molecules				
1	*VCAM1*	Vascular cell adhesion molecule 1 (VCAM-1)	CD106	Leukocyte-endothelial cell adhesion and signal transduction
19	*ICAM1*	Intercellular Adhesion Molecule 1 (ICAM-1)	CD54	Expressed on endothelial cells and cells of the immune system. Binds to integrins of type CD11a or CD11b (CD18)

Table 1 (*continued*)

Chromosome location	Gene	Name	Other names	Main function[a]
1	*SELE*	E-selectin	CD62E, ELAM	Found in cytokine-stimulated endothelial cells, accumulation of blood leukocytes at sites of inflammation
1	*SELL*	L-selectin	CD62L, LAM1, LECAM1	Expressed by leukocytes to facilitate their migration into secondary lymphoid organs and inflammation sites
6	*VEGFA*	Vascular endothelial growth factor (VEGF)	Vascular permeability factor (VPF)	Facilitates leukocyte infiltration into the inflammation site
Genes involved in allograft injuries				
19	*FAS*	Fas cell surface death receptor	APO1, CD95, TNFR6	Apoptosis of Fas-positive cells
12	*IFNG*	Interferon gamma (IFNγ)	Type II interferon	Activates of macrophages, induces cytotoxic activities of other cells and apoptosis

[a] Information obtained from the Gene database (NCBI).

of recent reports. We revisit the physiology of the immune system in the context of solid organ transplantation, and highlight important players. We then focus on studies performed with a notable number of cases for the outcome studied, aiming to avoid a common problem in the vast body of literature in this field: underpowered studies that report significant findings without adjustment, and consequent reporting bias of positive findings at specific loci, which in turn often conflict among the totality of positive reports. Among these studies, we highlight promising loci. At present, these require replication, and if confirmed relevant, testing in prospective trials to determine their usefulness as predictive markers.

2. Candidate genes

Proteins related to the immune response in the context of allograft transplantation whose genes are subsequently discussed in this review are listed in Table 1. Genes were selected based on association studies related to outcomes of success in renal transplantation. The loci studied are presented in Tables 2 and 3: Table 3 lists the most commonly studied panel of classic cytokine loci, while Table 2 extends the list of genes and presents less commonly studied loci.

2.1. Genes related to initial T cell activation

2.1.1. Histocompatibility leukocyte antigens (HLA)

Allograft rejection (and particularly humoral rejection) originates primarily due to HLA mismatch between the donor and recipient. Certain HLA mismatched transplants achieve long term function without evidence of humoral rejection, suggesting differential immunogenicity of HLA mismatches. One explanation might relate to regulators of HLA gene expression. The major histocompatibility complex class II transactivator, a master regulator of the HLA class II, is coded by *CIITA* which contains a Single Nucleotide Polymorphism (SNP) found to be associated with donor-specific human leucocyte antigen antibody production post-transplantation [6] (Table 3).

2.1.2. Co-stimulatory signals

The immune response leading to allograft rejection involves T cell activation triggered by antigen recognition through the T-cell receptor (TCR). This is reinforced by engagement of co-stimulatory molecules (CD28 and its ligands CD80 and CD86), known as the co-stimulatory signal, or signal 2 [7].

CTLA-4 is a CD28 homologue and is thus a negative regulator of T-cell proliferation signals (i.e. is an anti-proliferative signal) [3]. Several genetic variations in *CTLA4* gene have been tentatively linked to poor clinical outcomes in solid organ transplantation (acute rejection, steroid resistant acute rejection, delayed graft function, see below and in Table 3). Regarding CD28, one study focused on a single polymorphism in relation to acute rejection [8] (Table 3).

Following TCR engagement, the interaction between CD40 Ligand (CD40L, or CD154) and CD40 is the next critical event. CD40 is expressed on antigen-presenting cells and B lymphocytes, whereas CD40L is expressed on T lymphocytes. Their engagement on T lymphocytes induces IL-2 production, followed by evolution of CD8 + T cells into cytotoxic T cells (CTLs). CD40 is also important for B cells, monocyte, macrophage, and leukocyte functions in the context of the immune response (2). *CD40LG* was investigated as a candidate gene in one study concerning acute renal rejection but no association was found [9].

2.1.3. T cell receptor (TCR) regulators

Certain enzymes serve as negative regulators of T cells. The protein tyrosine phosphatase, non receptor type 22 (PTPN22) functions as a regulator of TCR-signal transduction by removing phosphate groups from tyrosine residues on intracellular proteins. A specific locus in the *PTPN22* gene has been investigated with respect to long-term allograft failure but no association was found [10] (Table 3).

2.2. Cytokine growth factors promoting T cell activation

There are two main sub groups of cytokines driving the expansion and differentiation of CD4 + T Cells in TH1, TH2, TH17 or regulatory T cells: pro- and anti-inflammatory cytokines.

The role of these cytokines in acute rejection or induction of graft tolerance is linked to the balance between TH1 and TH2 cells. TH2 lymphocytes facilitate tolerance by secreting anti-inflammatory IL-4 and IL-10 (inhibiting macrophages activation), whereas TH1 lymphocytes contribute to inflammation by secreting IL-2, IL-12, Tumor Necrosis Factor-alpha (TNFα) and Interferon gamma (IFNγ) [11]. The genes of these cytokines have been the focus of numerous genetic studies in solid organ transplantation: findings are summarized in Tables 2 and 3 and will be addressed in detail later in this review.

IL-2 promotes CD4 + and CD8 + T cells proliferation and differentiation. Its receptor (IL-2R) consists of 3 subunits, which modulate its affinity with IL-2: the high affinity α-chain subunit (CD25, coded by *IL2RA*); the β-chain subunit (CD122, coded by *IL2RB*) and the common γ subunit.

IL-17A and its homologue IL17F, critical cytokines responsible for Th17 cell reaction involved in inflammation, have been studied as candidate genes in kidney transplantation outcome and several SNPs in *IL17* have associated with outcomes (acute rejection and graft failure) [12–14] (Table 3).

Finally, TNFα is produced by activated macrophages but also by CD4 + T- and NK-cells. It is involved in inflammation, activating endothelial cells, up-regulating cell adhesion molecules and participating of the recruitment of different leukocytes [15]. A specific polymorphism in *TNFA* has been widely tested for association with renal transplant outcomes (Table 2) and will be discussed in detail below. Other loci have likewise been tested (Table 3).

Table 2
Classic cytokine polymorphic loci tested for association with renal transplant outcomes. Positive associations were considered as reported by authors.

Gene	Common name	dbSNP	No association	Association
IFNG	+874 A/T, UTR5644	rs2430561	[74,47,75,44,70,76,53,71,77-79,33,80-82,68,83,28]	[84,42,72,85–89]
IL10	−1082 G/A	rs1800896	[40,2,65,90-92,47,27,42,9,45,70,76,93,43,52,71,46,62,63,77,79,85,86,81,82,94,95]	[66,58,96-98,74,84,75,44,72,21,80,73,68,83]
IL10	−819 C/T	rs1800871	[40,2,96,65,90-92,47,75,27,42,45,70,93,71,46,62,63,77,85,81,82,94,28]	[84,44,21,80,68,83]
IL10	−592, 571 C/A	rs1800872	[40,2,96,65,90-92,47,75,27,42,45,70,93,43,71,77,78,85,81,82,94,95,28]	[84,44,21,62,80,68,83]
IL1A	−889 C/T	rs1800587	[40,2,49,75,85,80,81]	
IL1B	−511 C/T	rs16944	[40,2,75,99,46,85,80,94]	
IL1B	+3954, +3962 C/T	rs1143634	[40,2,75,99,85,100,80,94,28]	[46]
IL2	−330 T/G	rs2069762	[96,84,75,42,60,101,46,62,64,85,81,89,95]	[102,78,94]
IL4	−590 T/C	rs2243250	[40,2,90,49,75,93,64,78,85,89,94]	[98]
IL6	−174 G/C	rs1800795	[40,103,65,90,74,84,75,42,44,45,70,43,52,46,100,80,54,81,94,68,83,28]	[2,47,104,60,21,71,64,85,6,82,89,105]
TGFB	+869 C/T, +29, Leu10Pro, c10	rs1800470	[40,58,2,65,92,47,75,27,44,9,106,70,93,53,46,62,77,78,107,85,86,80,81,89,94,105,83]	[108,109,84,42,59,110,21,111,71,82,68]
TGFB	+915 G/C, Arg25Pro, +74, c25	rs1800471	[40,58,65,98,74,108,92,47,75,27,42,44,9,70,93,53,71,46,62,77,78,85,80,94,105,83,95]	[109,84,59,72,21,106,111,82,28,68]
TNFA	−308 G/A, TNF 1/2	rs1800629	[40,2,103,90,98,91,74,84,92,47,75,42,9,60,76,43,52,53,77-79,50,85,86,80-82,28,83]	[66,69,58,65,49,67,27,59,44,72,21,101,70,71,46,62,64,63,73,68,61]

[66] Sankaran 1999
[69] Poli 2000
[40] Marshall 2000
[58] Pelletier 2000
[2] Marshall 2001
[98] Poole 2001
[91] Hahn 2002
[74] Hutchings 2002
[108] Iñigo 2003
[109] Ochsner 2002
[102] Morgun 2003
[84] McDaniel 2003
[92] Melk 2003
[49] Lee 2004
[47] Müller-Steinhardt 2002
[104] Müller-Steinhardt 2004
[75] Uboldi de Capei 2004
[67] Wramner 2004
[27] Mytilineos 2004
[42] Hoffman 2004
[59] Park 2004
[44] Alakulppi 2004
[110] Chow 2005
[9] Dmitrienko 2005
[45] Loucaidou 2005
[60] Pawlik 2005
[72] Tinckam 2005
[21] Lacha 2005
[101] Pawlik 2005
[99] Manchanda 2006
[106] Hueso 2006
[70] Gendzekhadze 2006
[76] Azarpira 2006
[93] Amirzargar 2007
[111] Li 2007
[43] Alakulppi 2008
[52] Breulmann 2007
[103] Reviron 2001
[96] George 2001
[65] Gandhi 2001 (assumed loci based on commercial tray)
[97] Asderakis 2001
[90] Cartwright 2001
[53] Brabcova 2007
[71] Nikolova 2008
[46] Manchanda 2008
[62] Grinyó 2008
[64] Pawlik 2008
[63] Mendoza-Carrera 2008
[77] Tajik 2006
[78] Satoh 2007
[107] Cho 2008
[79] Azarpira 2008
[50] Israni 2008
[33] Singh 2009
[85] Lobashevsky 2009
[6] Martin 2009
[100] Krajewska 2009
[86] Omrani 2010
[80] Khan 2010
[54] Sánchez-Velasco 2010
[87] Crispim 2010
[81] Oetting 2011
[88] Zibar 2011
[82] Kocierz 2011
[89] Karimi 2012
[28] Jiménez-Sousa 2012
[112] Park 2011
[94] Seyhun 2012
[73] Mandegary 2013
[68] Dhaouadi 2013
[105] La Manna 2013
[61] El-Gezawy 2013
[83] Gaafar 2014
[95] Chen 2014

Authors, ordered by year published.

2.3. Genes related to the innate immune response

Proteins of the innate immune system may affect the longevity of the transplanted organ. Toll Like Receptors (TLRs) may be activated in a variety of circumstances. Ischemia-reperfusion creates a milieu of inflammation in the organ producing "danger signals" that activate TLRs, leading to an increased production of mRNA levels of certain cytokines (IL-1, IL-6, IL-8, IL-10 and IFNγ).

Furthermore, TLR expression of antigen presenting cells (APCs) may regulate the co-stimulatory signal and consequently influence the activation of the antigen-specific adaptive immune response [16]. The TLR family is composed of 11 members, activating different intracellular events through signal transduction: production of cytokines, chemokines and cellular membrane proteins related to the inflammatory responses. TLR4 and its co-receptor CD14, are believed to initiate inflammation and tissue injury by responding to many various ligands (CD14 recognizes bacterial components) [17]. The complement system contributes an important element of the innate immune system, but also plays a role in adaptive immunity: complement component 3 (*C3*) plays a central role in the activation cascade. Polymorphisms in *TLR2*, *TLR4*, *TLR9*, *CD14* and *C3* have been tested for associations with kidney transplant outcomes (see Table 3 for references).

Two cytokines involved in the innate immune response and which have been tested for association in renal transplantation are IL-1 and IL-6 (Tables 2 and 3).

The pro-inflammatory cytokine IL-1 exists on two major isoforms: IL-1α and IL-1β, coded by *IL1A* and *IL1B* respectively. IL-1α is translated into a biologically active form, whereas IL-1β has no biological activity until it is processed by caspase-1.

The IL-1 receptor antagonist, IL1RA (coded by *IL1RN*) is an IL1 signal regulator: it is produced in response to the same stimuli that lead to IL-1 production.

IL-6 has been the focus of numerous association studies (Tables 2 and 3). It is multifunctional, involved in leukocyte trafficking, T-cell proliferation, B-cell differentiation and survival. It is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli during systemic inflammation (including IL-1, IL-17 and TNFα).

2.4. Genes related to the effector phase of rejection (graft infiltration and injury)

2.4.1. Genes related to the graft infiltration

The infiltration of leukocytes into the site of tissue damage is an important part of the allograft rejection process. Extravasation of leukocytes from the blood to the site of inflammation is regulated by several protein families, including selectins, integrins, chemokines and chemokine receptors, whose expression is upregulated at the site of inflammation.

The interaction between selectins is the first step in the contact between the leukocyte and the blood vessel, allowing to the rolling of the immune cell along the vascular endothelium at the inflammation area. Endothelial cells express E-selectin (coded by *SELE*), while leucocytes express L-selectin (coded by *SELL*). Two groups explored the influence of the variability in *SELE* and *SELL* on acute renal rejection [18,19] (Table 3).

Subsequent interaction between chemokines and their receptors induces strong adhesion of leukocytes with endothelial cells.

The different roles and involvement of chemokines and their receptors in kidney diseases have been reviewed by Panzer and colleagues [20]. Two main families will be discussed here: the C–X–C and the C–C chemokine family (whose genes cluster at chromosome 14 and 17 respectively). Each chemokine has different primary target cells. For example, CCL2 (also known as MCP-1) targets monocytes, T cells, basophils, and natural killer (NK) cells, whereas CCL5 (also known as RANTES) targets eosinophils or basophils. The genetic variability of these chemokines and theirs receptors has been studied in the context of deterioration of graft function (*CCL5* and *CCL2*) [21], recurrent acute rejection (CCL5) [22] and premature kidney graft failure (CCL2) [23] (see Table 3).

Genes coding for Intercellular Adhesion Molecule 1 (*ICAM1*) and vascular cell adhesion molecule-1 (*VCAM-1*) have also been identified as candidates and explored (see Table 3 for references).

In addition to it's well known role in vasculogenesis and angiogenesis, vascular endothelial growth factor (VEGF) contributes to the local inflammatory processes that facilitate leukocyte infiltration. Several authors have investigated *VEGFA* as a candidate gene in the context of kidney transplantation (see Table 3 for references).

2.4.2. Genes involved in allograft injuries

Allograft destruction by activated T cells occurs via two major cytotoxic mechanisms: the release of perforin/granzyme in cytoplasmic granules of CD8 + CTLs and NK cells, and through the Fas/Fas ligand system in CD4 + CTLs. Activated macrophages, neutrophils and eosinophils contribute additionally.

The binding of Fas to its ligand (FasL) results in trimerization of Fas and apoptosis of Fas-positive cells. Increased expression of cell-surface Fas has been observed in acute rejection [24]. At least one study has investigated FAS as a candidate gene in kidney transplantation (Table 3).

IFNγ is produced by both adaptive and innate immune cells (e.g. NK cells, NKT cells, macrophages, myelomonocytic cells, TH1 cells, cytotoxic T lymphocytes, and B cells) and has distinct roles: on the one hand, it promotes the development of the TH1 response, regulates MHC class I, II and antigen presentation. On the other hand, it activates macrophages, the cytotoxic activities of other cells, and induces apoptosis [25]. It may contribute to the severity of the rejection episode by stimulating neopterin by monocytes derived macrophages, which are also effectors of tissue damage in the acute rejection process [26]. Association studies with this gene are reported in Table 2 and discussed below.

3. Association between genetic variation in immune response-related genes and outcomes in kidney transplantation

A very large number of short genetic variations (mostly SNPs and short insertion/deletions) in the above-mentioned genes have been studied in the context of success of the kidney allograft. In most cases those polymorphisms have been purported to have functional consequences, however these are likely to be context specific. Many candidate polymorphisms have been ascribed phenotypes and inheritance models based on specific in vitro or in vivo scenarios, which may not be relevant in the context of solid organ transplantation.

Much of this work in determining polymorphism candidates was performed prior to the Human Genome and HapMap Projects and has lead to a vast body of work using the same loci: this work continues despite the opportunities that these projects provide, and the choice of candidate polymorphism to represent these justified candidate genes might not be optimal. Furthermore, even if some of the polymorphisms in these candidate loci do indeed have functional and measurable consequences, for the most part, at present, none that have been replicated have emerged to impart an effect size that would lead to a clinical consequence with utility as a marker to predict outcomes. Below we focus on studies with a large number of cases for the phenotype studied: we arbitrarily chose approximately 100 cases as a threshold. This arbitrary choice reflects a number we thought was substantial. More precise calculations based on power depend on the minor allele frequency of each variant (which differs between loci) and some idea of effect size (which is often unknown), thus would be difficult to achieve.

Table 2 lists the genetic variations most commonly investigated. They are located in a panel of 9 genes. Table 3 lists the less commonly studied loci.

3.1. Positive associations in kidney transplant recipients

Perhaps the largest cohort in a single publication to-date involved 2298 primary transplant recipients and 1901 repeat transplants [27].

Of the primary transplant recipients, there were presumably 237 cases of graft failure after the first year, and of the repeat transplant 288, though these numbers were extrapolated from the presented percentages of graft survival and may not be exact due to censorship for death. Nonetheless, this represents a very large number of cases among published reports on this topic. This work was performed by the Collaborative Transplant Study group, an international registry. Only Caucasian participants were included, and all genotyped loci exhibited Hardy–Weinberg equilibrium. The authors grouped patients into presumed phenotypes of cytokine expression levels based on *IL10* haplotypes (comprising three SNPs: rs1800896 (−1082), rs3021097 (−819) and rs1800872 (−592)), two *TGFB1* SNPs in codon 10 (rs1800470; c10) and 25 (rs1800471; c25), one SNP in *TNFA* (rs1800629; −308) and one in *IL4R* (rs1801275: +1902).

No associations between the different presumed phenotypes and graft survival were found in first transplant recipients for the loci tested ([27] in Tables 2 and 3). Repeat transplant recipients with the *TNFA* rs1800629 (−308) A/A "high producer" genotype presented lower graft survival. This was significant at both 1 and 3 years post-transplant following correction for multiple testing in univariate

Table 3
Polymorphic loci in immune system genes, studied with respect to outcomes of success in the context of kidney transplantation. Positive associations were considered as reported by authors. Common names of loci are listed as reported by authors. All attempts were made to accurately retrieve rs identifiers for loci in order to consolidate reports.

Common name	dbSNP	No association	Associations
Cytokines and receptors			
IL1R1 −970 C/T			[45]
IL1R1 pst1 1970 C/T	rs2234650	[40,2,75,85,80]	
IL1RA 86 bp VNTR			[99]
IL1RN mspa1 11100 T/C	rs315952	[40,2,75,85,80]	
IL1RN VNTR 240/410 (intron 2)		[46]	
IL1RN A/G	rs2234676	[28]	
IL1RN C/T	rs419598	[28]	
IL2 + 166 G/T	rs2069763	[75,62,85,112]	[94]
IL2–IL21 intergenic	rs6822844	[113]	
IL2RB c.1173C/A	rs228942	[95]	[112]
IL2RB c.750C/T	rs228953	[95]	[112]
IL3 C132T, Pro27Ser	rs40401		[114]
IL3 (−1107 from 5′UTR)	rs181781		[114]
IL3 (−1484 from 5′UTR)	rs2073506		[114]
IL4 1098 T/G	rs2243248	[75,93,33,28,83]	
IL4 33 T/C	rs2070874	[33,28,83]	[75,93]
IL4 VNTR B1B1/B2B2		[46]	
IL4R +1902 G/A, Q576R Gln/Arg	rs1801275	[40,2,75,27,85,28]	
IL6 − 572 G/A	rs1800796	[28]	[104]
IL6 − 597 G/C	rs1800797		[104]
IL6 + 565 G/A, nt565	rs1800797	[75,28,33,83]	
IL6 3247 G/A		[40]	
IL8 -251 A/T	rs 4073		[33]
CXCR1 −2668 G/A	rs2671222		[18]
CXCR2 −8939 C/T	rs4674258	[18]	
CXCR2 1208 T/C	rs 1126579	[18]	
IL10 A	rs3024493	[50]	
IL10 A	rs1554286	[50]	
IL10 A	rs2222202	[50]	
IL10 C	rs3024498	[50]	
IL10 C	rs1878672	[50]	
IL10 G	rs3021094	[50]	
IL10 T	rs3024494	[50]	
IL10 −851 C/T	rs1800894	[62]	
IL10.G microsatelites			[115] (G12)
IL10.R microsatelites		[115] (G12)	
IL12B -1188 A/C	rs3212227	[75,78,80,26,116]	[85]
IL17 −197 A/G	rs2275913	[12]	
IL17F 6329 G/A	rs766748	[13]	
IL17F −1507 G/A	rs1889570	[13]	
IL17F 7384 A/G	rs2397084	[13]	
IL17F 7470 G/A	rs11465553	[13]	
IL17F 7489 A/G	rs763780		[13]
IL18 −137 G/C	rs187238	[117]	[30,118]
IL18 −607 C/A	rs1946518		[30,117]
IL21 5250 C/T	rs4833837	[12]	
IL21 + 1472 G/T	rs2055979	[12]	
IL23R c.309 C/A	rs10889677		[12]
TNFA −1031, −1032 T/C	rs1799964	[59,45]	
TNFA −238 G/A	rs361525	[40,2,75,27,59,78,85–87]	
TNFA −857, −859 C/T	rs1799724	[59,45]	
TNFA −863, −865 C/A	rs1800630	[59,45]	
TNFA +488 A/G		[2,40]	
TNFA A	rs3091257	[50]	
TNFA a microsatellite			[96] (a9), [119] (a9)
TNFA d microsatellite		[96]	[119] (4)

Table 3 (*continued*)

Common name	dbSNP	No association	Associations
TNFA G	rs3093662	[50]	[50] (uncorrected)
LTA 249 A/G (intron 1)	rs909253	[2,40]	
LTA 365 C/G (intron 1)	rs746868	[2,40]	
LTA 720 C/A (exon 3)	rs1041981	[2,40]	
TGFB1 −509 C/T	rs1800469	[2,40,78,107]	[108]
TGFB1 −880 G/A		[2,40]	
TGFB1 −800 G/A	rs1800468	[108]	
TGFB1 A	rs1800472	[50]	
TGFB1 C	rs1982073	[50]	
TGFB1 C-del (deletion)		[46]	
TGFBR2 C/G promoter	rs764522		
TGFBR2 G/A promoter	rs3087465	[120]	
TGFBR2 Asn389Asn (exon 3)	rs2228048	[120]	
IFNG12bp microsatelite	rs3138557	[58,90,9]	[97] (12CA), [63] (12CA)
Chemokines and receptors			
CCL2 (MCP-1) −2518 G/A	rs1024611	[61,53]	[21,23,121]
CCL2 C/T	rs4586	[28]	
CCL5 (RANTES) −109 T/C		[53]	[21]
CCL5 (RANTES) −28 C/G	rs2280788	[21,53,22]	
CCL5 (RANTES) −403 G/A	rs2107538	[21,53,28]	[22]
CCL5 (RANTES) In1.1 T/C (intron 1)	rs2280789	[22]	
CCR2 V64I, +190G/A, +/64I	rs1799864	[53,23,42,121,122]	[33,34,37,19,123,36]
CCR5 −32, delta32, Δ32	rs333	[53,33,34,37,35,19,123,122,36]	[87,32]
CCR5 −59029 A/G		[19,123,36]	[34,42,37,35]
CXCR4 C/T	rs2228014	[124]	
CX3CR1 V249I		[34]	
CX3CR1 T280M		[34]	
SDF1 G/A	rs1801157		[124]
Co-stimulatory molecules			
CTLA4 −1147 C/T	rs16840252	[125]	
CTLA4 +9 A/G, Thr17Ala	rs231775	[9,10]	[70,125,126]
CTLA4 −1661 A/G	rs4553808	[70]	
CTLA4 −1722 T/C	rs733618	[70]	
CTLA4 −318 C/T	rs5742909	[9,70,125]	
CTLA4 (AT)n (exon 3) 22 alleles		[127]	
CD28 +17 T/C IVS3	rs3116496		[8]
CD40LG 21-27 bp microsatelite		[9]	
Adhesion molecules			
ICAM1 G/A exon 6		[19]	
ICAM1 R241G, Gly152Arg	rs1799969	[63,87,28]	
ICAM1 A/G E469K, Lys469Glu	rs5498	[63,87,28]	[128]
ICAM1 G/R (exon 4)		[19]	
VCAM1 T/ C	rs3170794	[128]	
VCAM1 T/ C	rs1041163	[128]	
SELE 1402 C/T, His468Tyr	rs5368	[18]	
SELE G/T (exon 2)		[19]	
SELE 128 S/R, Ser149Arg (exon 4)		[19]	
SELE 554 L/F, Leu575Phe (exon 11)		[19]	
SELL −206 F/L, Phe206Leu	rs1131498	[19]	
SELL −642 A/G	rs2205849	[18]	
Innate immune system			
C3 Arg80Gly, S/F			[51]
TLR2 A/T (−16934)	rs4696480	[28]	
TLR4 C/T (Thr397Ile)	rs4986791	[28]	
TLR4 D299G, Asp299Gly		[129,17]	[130,131]
TLR4 T399I, Thr399Ile		[129]	[130,131]
TLR9 −1486 T/C	rs187084		[132]
TLR9 2848 G/A	rs352140	[132]	
CD14 −159 C/T		[17]	
CD14 −260 T/C	rs2569190	[133]	
T-cell activation/regulation			
CIITA −168 A/G	rs3087456	[6]	
CIITA 1614 G/C	rs4774		[6]
PTPN22 1858 C/T	rs2476601	[10]	
Other			
FAS -670 G/A		[105]	
PTPRC (CD45) 77 C/G (exon 4)	rs17612648	[9]	
VEGFA −1154 A/G	rs1570360	[31]	[29,30]
VEGFA −2578 C/A	rs699947		[28,29,31,30]
VEGFA −460 T/C	rs833061	[28]	
VEGFA −7 C/T	rs25648	[31]	
VEGFA 936 C/T 3′UTR			[39]

analyses. Significance was maintained in HLA-DRB1 mismatched recipients (1–2 mismatches, n = 1045) but not in matched recipients (n = 46).

In multivariate Cox regression analysis the *TNFA* rs1800629 (−308) A/A "high producer" genotype was associated with relative risk of 1.96 (95% CI: 1.23–3.11; p = 0.0047), presumably after the first year, and remained significant by the third year. *TGFB1* "high producer" haplotype, *versus* "intermediate" and "low producer" haplotypes combined presented higher transplant survival, but only after the first year. In the Cox model this represented a relative risk of 1.49 (95% CI: 1.15–1.92; p = 0.0026). The authors acknowledge the limitation of working with data from a large registry, and that testing clinical outcomes such as acute rejection or delayed graft function is difficult as they are unverifiable: for this reason graft survival with censorship for loss to follow-up was the approach taken. Furthermore, details of variables, including acute rejection and delayed graft function, would not have been included in multivariable analyses for graft survival.

Jiménez-Sousa and colleagues explored chronic renal allograft dysfunction, defined as ≥30% of the inverse of creatinine after the third month of transplantation, versus the highest value of the first three months (158 cases; 118 controls) [28]. Thirty-eight loci in 10 immune related genes were genotyped ([28] in Tables 2 and 3). The loci were primarily in promoter regions, and were included if functional consequences could be determined using a variety of in silico methods. They found three significant associations, following exploration of possible genetic models of inheritance, and adjusted findings in multivariable analysis.

TGFB1 rs1800471 (G/C *versus* G/G) and *VEGFA* rs699947 (A/C–A/A *versus* C/C) associated with an increased risk of chronic renal allograft dysfunction (OR = 2.65, 95% CI: 1.09-6.47; p = 0.025 and OR = 1.80, 95% CI: 1.02–3.20; p = 0.044, respectively).

Correction for multiple testing was performed by the Stratified False Discovery Rate software. *VEGFA* rs699947 has been found to associate with other kidney transplant outcomes in smaller cohorts and with varying methodologies in analyses among reports (acute rejection: [29,30]; graft survival: [31]; see Table 3). These authors did not apply corrections for multiple tests.

Fischereder et al. report improved graft survival in *CCR5* Δ32 (i.e. a deletion of 32 nucleotides in CCR5; rs333) homozygous carriers compared to heterozygotes and non carriers: only one of 21 (4.7%) individuals lost their graft in the follow up period, compared to 87 of 555 in the other group (15.7%) (HR = 0.367, 95% CI: 0.157–0.859; log-rank p = 0.033) [32] (see Table 3). However, from the Kaplan–Meier plot presented it is clear that a substantial proportion of both groups are not represented in data beyond 5 years of follow up, and at this time point it is difficult to tell whether the difference in graft survival between the groups would have been significant.

It also raises the question whether bias occurred in following the known *CCR5* Δ32 homozygous carriers more closely compared to larger cohort. The frequency of rejection episodes was similar between the two groups. The deletion is rare and several groups reporting lack of associations did not detect homozygous carriers [17,33–37] (Table 3).

Oetting et al. performed a validation study for frequently 21 reported loci (see Tables 2 and 3 for loci related to the immune genes) [38]. A total of 585 patients were genotyped, and there were 98 cases of acute

Notes to Table 3:
Authors from Table 2 that tested additional loci are included here using the same order. Additional reports are from the following authors:
[113] Asano 1997.
[114] Kobayashi 1999.
[32] Fischereder 2001.
[29] Shahbazi 2001.
[34] Abdi 2002.
[23] Krüger 2002.
[42] Hoffmann 2004.
[115] Viklický 2004.
[31] Lemos 2005.
[116] Ducloux 2005.
[51] Brown 2006.
[117] Palmer 2006.
[118] Kolesar 2007.
[22] Krüger 2007.
[119] Nogueira 2007.
[37] Yigit 2007.
[39] Günesacar 2007.
[26] Chin 2008.
[120] Kang 2008.
[121] Kim 2008.
[122] Hoffmann 2009.
[35] Cha 2009.
[123] Kim 2010.
[124] Krichen 2010.
[125] Lee 2010.
[18] Ro 2011.
[19] Krichen 2011.
[126] Lee 2011.
[127] Gorgi 2011.
[30] Mittal 2011.
[128] Azmandian 2012.
[36] Firasat 2012.
[129] Domański 2012.
[12] Karimi 2014.
[130] Kim 2013.
[10] Kłoda 2013.
[131] Kłoda b 2013.
[132] Kim b 2013.
[17] Krichen 2013
[133] Kwiatkowska 2014.
[13] Park 2014.
[8] Pawlik 2014.

rejection in the first 12 months post-transplantation. Loci were tested at three time-points to acute rejection (1 month, 6 months 12 months).

The authors make a case against correction for multiple testing, and instead applied a sum of squared score test, however this approach permits a p value threshold of 0.0615 and is unconvincing. For immune related genes, *CCR5* Δ32 associated with acute rejection at six months only. While Fischereder et al. report a protective effect of this deletion for homozygous carriers (Del/Del), Oetting et al. grouped heterozygous and homozygous carriers (Wt/Wt *versus* Wt/Del or Del/Del, OR = 2.33, 95% CI: 1.08–5.02; p = 0.0316). Both findings are in the same direction for a protective effect of the variant (Δ32) allele.

Gunesacar et al. genotyped the single SNP *VEGFA* rs3025039 (reported as +936 C/T), located in the 3′ untranslated region in cases who had lost their graft in the first year post-transplant, and controls with a well functioning graft at the same time point (n = 265 cases, n = 290 controls) [39]. Subjects were sourced from the Collaborative Transplant Study bio-bank, were Caucasian and were all primary kidney recipients receiving deceased donor kidneys.

A protective effect was detected among heterozygotes at this locus (OR = 0.57, 95% CI: 0.35–0.91; p = 0.019). A dose effect was not evident among TT carriers, but may be due to lack of power.

3.2. Positive associations in donor and recipient cohorts

Marshall et al. analyzed 22 polymorphisms in 11 cytokine genes in kidney transplant recipients (114 cases, 95 controls) [40] and 20 polymorphisms in 11 genes in cadaveric donors (77 cases, 68 controls) [41] (see Tables 2 and 3).

The phenotype considered was presence or absence of acute rejection in the first 30 days post transplantation: although this phenotype is somewhat limited and only applicable to the immediate post transplant period, the large number of cases defined by strict clinical criteria give weight to the findings, though the results are not generalizable. To cover the large number of tests considering various genetic models and haplotype combinations, the authors applied a two-set approach as a correction. No associations were found for recipients. In donors, however, the *IL6* promoter SNP rs1800795 (known as –174) associated with acute rejection (C/C vs G/C and G/G genotypes: OR = 8.67; p = 0.0002). This finding was significant regardless of HLA mismatch grouping. The two-set approach affirmed relevance in the context of multiple testing. In sub-group analyses steroid responsive rejections maintained significance, however steroid resistant rejection demonstrated an elevated degree of risk (compared to no rejection; cases = 33, controls = 68; OR = 15.96; p = 0.000007). Fifty-six donors provided kidneys to two distinct recipients: for the primary analysis one recipient was included and selected in a random fashion. The 56 remaining recipients allowed testing of the outcome to determine a positive predictive value in an independent, albeit small, group: the finding remained significant (PPV = 78%; p = 0.02).

The *IL6* rs1800795 (−174) C allele is reported to correspond to decreased IL-6 secretion, however the authors argue that linking genotype to *in vivo* phenotype is not straight forward, especially given its pleiotropic effects. They present an interesting set of arguments, but what is clear is that the finding is compelling.

Other authors that have tested this locus in donors did not find an association for acute rejection (see Table 2) in relatively large (>100 cases) [42,43] or in smaller [44–46] studies, thus it may be specific for the immediate post-transplant period, and for solely cadaver donors. Despite a small case number for the phenotype studied (n = 39, graft loss), Müller-Steinhardt and colleagues had complete 3 year data for their cohort of 158 kidney recipients [47]. They found *IL6* rs1800795 (−174) C allele carrying recipients (C/C–G/C) were at an increased risk (Bonferroni corrected p = 0.047). When this group re-examined their data testing additional *IL6* promoter polymorphisms (rs1800797: −597, rs1800796: −572) the risk estimate was strengthened: individuals homozygous for the wild-type allele at all three loci (G–G–G haplotype) exhibited superior graft survival at three years. Those with a mutant allele at any locus were at an 8-fold increased risk (95% CI: 1.8–34.6; p = 0.006).

Experimental data for the functional consequence of these loci demonstrates a complex scenario, and that genotyping *IL6* rs1800795 (−174) alone might miss the bigger picture [48]. Marshall et al. note that rs1800795 is located near two steroid response elements, and hence may influence outcomes in a context specific manner [40].

The effect size of IL6 SNPs seems notable and replication in an appropriate sized cohort might prove worthwhile to determine if this locus will be a clinically useful predictive marker.

Lee et al. tested three loci *IL1A* rs1800587 (−889 C/T), *IL4* rs2243250 (−590 C/T), *TNFA* rs1800629 (−308 G/A) (recipients: cases = 140, controls = 137; cadaveric donors: 122 = cases, 111 = controls) [49]. Cases were defined as having at least one acute rejection episode in the first post-transplant year, while controls had no such events in the first year. No associations were found for any of the loci. Sub-group analyses among HLA-DR mismatched transplants revealed *TNFA* rs1800629 (−308) A allele, only among donors, conferred an increased risk for rejection (cases = 75, controls = 45; RR = 1.4, p = 0.0395): a two-set approach was used to account for multiple testing.

Israni et al. constructed an impressive cross-sectional cohort comprising 616 recipients from the Delaware Valley region, and 349 recipients receiving the contralateral kidney identified through the United States Renal Data System (USRDS) registry [50]. The total cohort comprised 965 recipients and 512 donors. The phenotype examined was delayed graft function, defined as requiring dialysis in the first week post-transplant (up to 326 events were analyzed, depending on the loci tested). While most authors select candidate polymorphisms based on literature reports, this group attempted a tagging approach when possible, and aimed for loci with a minor allele frequency > 10% (number of loci per gene: *HMOX1*: 9, *IL10*: 7, *TNFA*: 3, *TP53:* 7, *TGFB1*: 2). *TGFB1* loci were selected based on reported functional consequence (*HMOX1* and *TP53* are apoptosis related genes). Only donors were genotyped: 256 donors contributed both kidneys (representing 512 recipients in the final analysis). Of these, 57% of recipient pairs had concordant outcomes: the authors report this as unexpected due to chance (p = 0.004, binomial exact test).

TNFA rs3093662 G versus A allele associated with delayed graft function following multivariable analysis (OR = 1.85, 95% CI: 1.16–2.96; p = 0.01), however this did not hold when a correction for multiple testing was applied.

Brown et al. genotyped the complement *C3* rs2230199 SNP ($Arg^{80}Gly$), designated Slow (S) and Fast (F) respectively, for the difference in electrophoretic motility imparted on the protein due to the amino acid change, in 513 pairs of Caucasian donors and recipients [51]. Donor genotypes proved of importance, but only when recipients did not carry the mutant allele: kidneys from donors with *C3* S/S versus *C3* F/F or F/S genotypes exhibited improved graft survival (hazard ratio = 2.21, 95% CI: 1.04–4.72; p = 0.04).

Other notable cohorts, exhibiting a large number of cases of the phenotype tested and where donors were genotyped include the ones from Hoffmann et al. [42] (donors only, loci in *IL2*, *IL6*, *IL10*, *TNFA*, *TGFB1*, *IFNG*, *CCR2*, *CCR5*; Tables 2 and 3) and Firasat et al. [36] (donors and recipients, loci in *CCR2* and *CCR5*; Table 3), however both papers suffer poor reporting or lack of strategy to address multiple testing. Hoffmann et al. genotyped 12 loci in 244 donors and report associations between *TGFB1* codon 10 variant (rs1800470) and *CCR5* rs1799987 (59029G/A) and acute rejection (approximately 109 episodes; p = 0.027 and p = 0.039 respectively) and *IFNG* rs2430561 (+874A/T) and biopsy-proven chronic allograft nephropathy (p < 0.008) [42]. The authors report applying a Bonferroni–Holm correction with Fisher's exact test in the methods, however the results that are reported used chi-square, linear regression and Kaplan–Meier methods and it is unclear how multiple testing was ultimately accounted for.

Firasat et al. genotyped up to 606 pairs donors and recipients (n = 157 episodes of rejection, biopsy proven) and report the G/G wild type genotype of *CCR2* rs1799864 ($V^{64}I$) in recipients to be associated with rejection (OR = 2.14, 95% CI = 1.2–3.7, p = 0.009): correction for multiple testing was not addressed [36].

3.3. Large cohorts with no associations at loci tested

We applied similar criteria for reports on lack of association, namely a large number of cases and a strategy to address multiple tests. Dmitrienko et al. analyzed loci in *CTLA4*, *TGFB1*, *IL10* or *TNFA*, and dinucleotide repeat polymorphisms in *IFNG* and *CD40L*, in 100 acute rejection cases, and 100 rejection free renal transplant recipients (Caucasian first kidney recipients, for events occurring in the first post-transplant year; Tables 2 and 3) [9]. No associations were found with acute rejection for single loci or allelic analyses for dinucleotide repeats in multivariable analyses. Associations with the *CD40L* -147 allele (rs not reported) and *TGFB1* c25 (rs1800471) and graft failure, a secondary outcome measure, require confirmation as the authors report, particularly as this phenotype was not used for constructing the case control cohort. Breulmann and colleagues genotyped *IL10* rs1800896 (−1082), *TNFA* rs1800629 (−308), *IL6* rs1800795 (−174), grouping by predicted phenotypes at two levels, in a large cohort (224 consecutive patients, rejection cases = 115, graft failure = 33) and found no significant associations with rejection [52] (Tables 2 and 3). Alakulppi et al. typed *TNFA* rs1800629 (−308), *IL10* rs1800872 (−592), rs1800896 (−1082) and *IL6* rs1800795 (−174), as well as other loci in genes with a functional role in thrombogenesis (total of 11 loci, see Tables 2 and 3 for immune genes) [43]. They included 772 recipients, and 462 donors; the number of cases with rejection was 122.

Correction for multiple testing was applied and no locus was found associated with rejection, or the other clinical outcomes tested, for neither donors nor recipients. Brabcova and colleagues typed 9 loci in immune system genes *TNFA* rs1800629 (−308), *CCL2* rs1024611 (−2518), *CCL5* rs2107538 (−403), −109 (no rs reported) and rs2280788 (−28), *CCR2* rs1799864 (+190G/A), *IFNG* rs2430561 (+874A/T), *TGFB1* rs1800470 (c10) and rs1800471 (c25) (total number of recipients = 436; chronic allograft nephropathy cases = 122, cases with sub-clinical rejection = 38, acute rejection cases = 190), and found no associations [53] (Tables 2 and 3). Sánchez-Velasco and colleagues genotyped *IL6* rs1800795 (−174) in 335 kidney recipients (cases of acute rejection = 133, cases of chronic allograft nephropathy = 115) and found no associations [54] (Tables 2 and 3).

3.4. Meta-analyses of published associations

To make sense of this vast body of literature, several authors have performed meta-analyses at the most frequently studied loci.

Thakkinstian and colleagues attempted to achieve individual patient data for their meta-analysis in the kidney transplant setting by petitioning authors [55]. Five of 13 invited authors collaborated: these thirteen papers had passed pre-determined selection criteria. There was sufficient data to explore the effect of *TGFB1* rs1800470 (c10) (data representing 5 studies; 334 cases/325 controls), *TGFB1* rs1800471 (c25) (4 studies, 234 cases/205 controls), *TNFA* rs1800629 (−308) (4 studies, 350 cases/427 controls), *IL10* rs1800896 (−1082; 3 studies, 122 cases/117 controls) on transplant outcome. 'Poor outcome' was a composite of acute graft rejection, chronic allograft nephropathy, graft failure and chronic graft rejection thus muddying analyses. No association was found with any of these polymorphisms in univariate analyses.

Age ≥ 45, and ≥ 3 HLA mismatches associated with poor outcomes: a fixed-effect logistic model including these covariables revealed that *TGFB1* rs1800470 (c10) T/C vs T/T genotype increased risk, OR 1.5 (95% CI: OR: 1.0–2.2; p = 0.034; 325 cases, 334 controls). No effect on risk was found when C/C was compared to T/T carries making interpretation of this finding difficult (Cochrane Armitage test for trend, lack of dose effect despite a substantial number of CC heterozygotes). For *IL10* rs1800896 (−1082), this group included ORs from three additional studies to the individual patient data, achieving 352 cases and 302 controls. With and without adjustment for age and HLA mismatches, there was no significant association at this locus, however the authors report a trend: a minor dose effect can be observed, but is likely due to chance. Correction for multiple testing was not reported. Significant findings were reported for haplotype analyses of *TGFB1* and *IL10*, but are unconvincing.

Wu et al. performed a meta-analysis of loci in the *IL4* gene, limiting to studies reporting acute rejection, and explored various modes of inheritance (multiplicative model, Cochrane Armitage test for trend, dominant and recessive models) [56]. Pooled analyses (including heart, liver and kidney transplant) revealed no association for recipient *IL4* rs2243250 (−590 C/T) (492 cases and 721 controls; 7 studies of kidney, 2 of liver and 1 of heart transplants); recipient *IL4* rs2070874 (−33C/T) (98 cases and 220 controls; 2 studies in kidney, 1 in liver); and donor *IL4* rs2243250 (−590 C/T; 298 cases and 390 controls; in kidney (n = 4 studies) 4 and heart (n = 1) transplants). No significant associations emerged in sub-group analyses by ethnicity (Asian and Caucasian). Most of the data represented kidney transplant recipients, and there were no significant findings for these SNPs.

IL4 rs2243250 (−590 C/T) was associated with acute rejection of liver transplants (T/T + C/T vs. C/C: OR = 0.36, 95% CI 0.14–0.90; 77 cases, 152 controls). The p value for this association is not reported, but rather a p value for heterogeneity, which the authors deem acceptable. At the same time, it is not clear whether corrections for multiple testing were applied.

Ge and colleagues performed a meta-analysis of studies involving *TGFB1* c10 (rs1800470) and c25 (rs1800471) loci and acute rejection [57]. Among kidney transplant recipients (9 studies, 123 cases, 301 controls) there was no association for purported intermediate versus high production phenotypes. The significant findings reported globally were influenced by two studies in heart transplant recipients.

3.5. Notable associations: TNFA rs1800629 (−308)

In Table 2 of the most frequently studied loci, the balance between positive reports and negative reports of association largely favors the negative side. The exception is *TNFA* rs1800629 (−308). Associations have been found between this SNP and numerous outcomes in donors and recipients: acute rejection, recipients [21,44,46,58–63]; graft survival, recipients [27,64]; graft survival, donors [65]; associations in sub group analyses, recipients [66–68], associations in sub group analyses, donors [49]; associations with other phenotypes/multiple phenotypes [69–72]; donors: [73] (see Table 2).

Majority of reports of association implicate the *TNFA* rs1800629 (−308) A allele in acute rejection. While studies with a substantial number of cases found no association with the phenotypes tested [41, 43,52,53], Mytilineos and colleagues found an almost doubled risk for graft loss in cadaver kidney recipients, but not in primary kidney recipients, independent of HLA mismatching, and in a large Caucasian cohort [27]. In situations where *TNFA* rs1800629 (−308) has associated with an outcome in HLA mismatched subgroups, donor type may have been a primary reason.

Some authors report synergy for combinations of loci in *TNFA* and *IL10* in recipients: the original paper from Sankaran et al. is frequently reported and derives from an analysis in a cohort of 100 recipients and donors, where a large proportion received treatment for rejection [66]. The authors group controls as 0 or 1 rejection episode (n = 74), and cases as 2 or more (n = 21). All significant findings were in subgroup analyses, and in recipients only, and although justified by physiologically plausible explanations, there was no apparent correction for multiple testing. Marshall et al. did not corroborate these combinations in a larger cohort [40].

In their excellent review of cytokine gene polymorphisms and their functionality, Smith et al. present a case that the *TNFA* rs1800629 (−308) might not have a functional consequence, and might instead be a marker in linkage disequilibrium [48]. While there are numerous *TNFA* promoter polymorphisms, the authors present the possibility through reports of interesting experimental work that the functional polymorphism might even occur in the nearby *LTA* gene. If this locus does indeed represent a different functional polymorphism in *TNFA* or a nearby gene, ethnic origin is crucial and may be one of the reasons for discrepancies in findings.

4. Conclusion

The literature dedicated to determining associations between kidney transplant outcomes and genetic polymorphisms in immune system genes suffers from positive reports of associations, often from underpowered studies, which might in turn represent publication bias. We have attempted to highlight interesting findings from studies with a large number of cases, which typically have addressed the issue of multiple testing.

The role of the immune system in the context of transplant medicine in events such as acute rejection, delayed graft function, chronic allograft dysfunction and graft survival, among others, is complex and involves many genes. Of these, many are polymorphic, and there is a possibility that multiple loci have functional consequences. Strategic selection of loci may help to better interrogate candidate genes, for example tag-SNP approaches involving loci with a minor allele frequency greater than a threshold percentage, or in silico approaches in determining promoter and splice site variants. Typically these genes are highly conserved, with very few examples of polymorphisms influencing the protein sequence. Grouping rare SNPs in association studies might help to address the issue of rarity for loci that have a confirmed functional effect. However, multiple rare SNPs might not necessarily appear in individuals so as to affect the effect size in an incremental way.

The event outcomes are complex phenotypes and likely have variable and complex causes. Multivariable models including variables known to affect the outcome of interest are necessary. Although it is difficult to conceive confounding in associations related to genotype, multivariable analyses help in adjusting the observed effect, and may strengthen it, or reveal it to be weak.

There are various strategies to address the issue of multiple testing including the two-set approach and Bonferroni correction. In the difficulty of achieving appropriate sized case cohorts, Bonferroni correction may be too strict, while the two-set approach may lead to loss of power in very small case cohorts. Retrospective cohorts are difficult to reconstruct with complete data, and in particular lead to inadequate measure of the phenotype/outcome of interest, which may be falsely recorded as a case or unintentionally missed. Prospective cohorts require a minimum 95% participation to represent the population. Cross sectional case control selection requires that accurate data of variables known to affect the outcome be included. While genetic loci cannot be confounded in the traditional sense, these variables are necessary to adjust the measured effect size and place it in context. A case control design has the advantage of increasing the number of cases, and thus contributing greater power. While matching is a controversial topic, in transplant medicine matching allows accounting for a spectrum of variables without subsequent adjustment. Matching time-to-event in controls is one way to approximate similar experience of immune suppression and risk experience in controls.

A major concern is also to identify the most relevant phenotype to address in genetic association studies. New immunosuppressive regimens have considerably decreased acute rejection rates (at least in kidney transplantation), which make adequately powered studies difficult to undertake in restricted transplant populations. Alternately chronic dysfunction is an attractive phenotype to study since it addresses a particularly relevant long-term outcome. It is however very difficult to define consensually and homogeneously. Variation in phenotype selection among studies is a limit for replication and the identification of valuable markers.

We agree with other authors that a collaborative approach, with studies based on large populations, with uniform definition of phenotypes is warranted to reach a sufficient level of evidence [41].

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