Genetic susceptibility to delayed graft function following kidney transplantation: a systematic review of the literature

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ABSTRACT

Delayed graft function (DGF) is defined as the need for dialysis within 7 days following kidney transplantation (KTx). DGF is associated with increased costs, higher risk for acute rejection and decreased long-term graft function. Renal ischaemia/reperfusion (I/R) injury plays a major role in DGF occurrence. Single nucleotide polymorphisms (SNPs) in certain genes may aggravate kidney susceptibility to I/R injury, thereby worsening post-transplant outcomes. The present article proposes an extensive review of the literature about the putative impact of donor or recipient SNPs on DGF occurrence in kidney transplant recipients (KTRs). Among 30 relevant PubMed reports, 16 articles identified an association between 18 SNPs and DGF. These polymorphisms concern 14 different well-known genes and one not-yet-identified gene located on chromosome 18. They have been categorized into five groups according to the role of the corresponding proteins in I/R cascade: (i) oxidative stress, (ii) telomere shortening, (iii) chemokines, (iv) T-cell homeostasis and (v) metabolism of anti-inflammatory molecules. The remaining 14 studies failed to demonstrate any association between the studied SNPs and the occurrence of DGF. A better understanding of the genetic susceptibility to renal I/R injury may help prevent DGF and improve clinical outcomes in KTRs.

Keywords: delayed graft function, ischaemia/reperfusion, kidney transplantation, polymorphisms, renal allograft

INTRODUCTION

Delayed graft function (DGF) is a manifestation of acute kidney injury related to kidney transplantation (KTx). It has been defined as the requirement for dialysis within 7 days following KTx [1]. DGF causes increased risk for acute rejection (AR) and has been associated with poor long-term graft outcomes and additional costs [2]. Various immunological and non-immunological factors have been linked to DGF, including donor age, Human Leucocyte Antigen (HLA) compatibility, cold and warm ischaemia time, immunosuppressive regimen of induction and maintenance and dialysis vintage. Expanded criteria donors (ECDs) in KTx lead to an increased risk for DGF [3]. Still, the incidence of DGF in ECD recipients has progressively decreased over time from 35.2% in 2003 to 29.6% in 2011 in the USA, probably related to a better understanding of the donor risk profile along with improved allograft selection [3]. Cardiac death donors have also shown a higher rate of DGF [4]. Indeed, renal ischaemia/reperfusion (I/R) injury plays a critical role in DGF. I/R injury occurs when the blood...
supply to an organ is transiently disrupted and subsequently restored [5]. KTx necessarily conveys renal I/R, which prompts active preclinical and clinical research focusing on the prevention and/or attenuation of graft damage [6–9].

Besides the role of extrarenal factors in DGF, one may speculate that intrarenal characteristics may predispose the kidney allograft to injury. Global gene expression profiling captures such a complex process, thereby highlighting the putative implications of particular genes and metabolic cascades in renal I/R injury and DGF [8, 10, 11]. DGF-associated genes are implicated in pathways of oxidative stress, vasospasm, cytokine signalling, endothelial and epithelial cell injury, as well as innate and adaptive immunity. Some of these genes harbour single nucleotide polymorphisms (SNPs). By definition, SNPs correspond to the variation of only one base pair in one given gene, which may cause significant changes in the expression and/or activity of the corresponding protein. By extension, polymorphisms correspond to the coexistence of several distinct alleles in one given gene in a population. The haplotype is the combination of SNPs at multiple linked loci that are usually transmitted as a group from parent to child.

In 2008, Krüger et al. [12] summarized the literature about genetic polymorphisms and the fate of the transplanted organ, including the impact of both immunological and non-immunological cascades on graft survival, AR and the occurrence of chronic allograft nephropathy. Our present review focuses on DGF and aims to systematically detail the published reports about potential associations between polymorphisms in kidney donors and recipients and the occurrence of DGF.

MATERIALS AND METHODS

We systematically searched PubMed for articles published from the database’s inception date to May 2017 using the following keywords: ‘delayed graft function’ or ‘DGF’ or ‘ischaemia-reperfusion’ and ‘kidney’ or ‘renal’ and ‘alloraft’ or ‘transplantation’ and ‘polymorphisms’ or ‘SNP’. Furthermore, we reviewed the papers referenced in the ‘PubMed-related’ articles to identify additional candidate studies for which full-text English-language articles were available. Bibliographic references of both original investigations and review articles were then scrutinized. We included studies with the following quality criteria: (i) ≥50 patients (kidney recipients, donors or both), (ii) well-defined evaluation of DGF occurrence and outcomes and (iii) polymorphisms in molecules involved in I/R-related processes. The articles that did not reach these criteria were excluded. Careful attention was given to the genetic background of studied populations.

RESULTS

We found 45 relevant articles in the PubMed database using the above-defined keywords. Four of these were excluded because the studied polymorphisms concerned genes coding for proteins involved in pharmacodynamics and pharmacokinetics of immunosuppressive drugs. Eleven articles were excluded because they did not strictly focus on DGF. Among the remaining 30 articles, 16 found an association between 18 polymorphisms and DGF (Table 1). These polymorphisms were present in 11 different well-known genes and in one not-yet-identified gene located on chromosome 18. We categorized them into five groups according to the role of the corresponding proteins in I/R cascade: (i) oxidative stress, (ii) telomere shortening, (iii) chemokines, (iv) T-cell homeostasis and (v) metabolism of anti-inflammatory molecules. The remaining 14 studies failed to demonstrate any association between the studied polymorphisms and the occurrence of DGF. These data are summarized in Table 2.

Oxidative stress

GSTM1, GSTM3, GSTT1, GSTP1 and MnSOD polymorphisms. Glutathione S-transferases (GSTs) and manganese superoxide dismutase (MnSOD) contribute to protection against xenobiotic compounds, including immunosuppressive drugs in kidney transplant recipients (KTRs). GSTs and MnSOD are also involved in antioxidative reactions and in the regulation of apoptosis through direct protein–protein interactions. At the time of kidney reperfusion, GSTs and MnSOD are rapidly induced to scavenge reactive oxygen species (ROS) and prevent ROS-associated damage [13, 14]. St. Peter et al. [13] genotyped 229 British KTRs with ≥24 h of cold ischaemia and 104 of their respective donors. They focused on the polymorphisms of three classes of GSTs and MnSOD: GSTM1*A, GSTM1*B, GSTT1*I, GSTP1*A, GSTP1*B, GSTP1*C, GSTP1*D, MnSOD a14Aal and MnSOD a14Val. In kidney donors, the presence of homozygous GSTM1*B or heterozygous GSTM1*B with GSTM1 null or GSTM1*A was associated with a lower risk for DGF. In KTRs, no association was found between any enzyme polymorphism and DGF occurrence [13]. Singh et al. [14] enrolled 223 controls and 273 North Indian KTRs to study the impact of polymorphisms in three GST isoenzyme genes (GSTM1, GSTM3, GSTT1 and GSTP1) on early graft function. The authors observed that recipients with the rs1695 genotype GG of GSTP1 were at higher risk of DGF [14].

NADPH oxidase p22(phox) C242T polymorphism. p22(phox) is a polymorphic subunit of NADPH oxidase that plays a critical role in its activation and stabilization. NADPH oxidase is involved in the production of superoxide that triggers the inflammation in ischaemic kidneys [43, 16]. Mandegey et al. [16] enrolled 196 Iranian donor–recipient pairs to investigate the association between donors’ and recipients’ NADPH oxidase p22(phox) C242T polymorphism and AR, DGF and blood pressure levels in KTRs. Recipient’s p22(phox) 242T allele (CT + TT) was found to be a major risk factor for DGF, most probably via the overproduction of superoxide at the time of I/R [16].

Telomere shortening

A significant shortening in telomere length has been reported in ischaemic kidneys, which suggests I/R-accelerated tissue senescence [44]. Shorter telomeres have also been associated with a lower immune response [45]. Polymorphisms in hTERT, BICD1 and chromosome 18 interfere with telomere shortening. Kloda et al. studied rs2735940 hTERT, rs2630578 BICD1 and rs7235755 in chromosome 18 polymorphisms in 119 Polish kidney allografts [17] and corresponding recipients [18] as well as in an independent cohort of Polish recipient–donor pairs [19].
Table 1. Polymorphisms associated with DGF

| Polymorphism                          | Gene      | Role of the molecule                                         | n donors versus recipients | Nationality | Outcome in DGF                                   | Reference |
|--------------------------------------|-----------|--------------------------------------------------------------|----------------------------|-------------|-------------------------------------------------|-----------|
| Cascade of the oxidative stress      |           |                                                             |                            |             |                                                 |           |
| GSTM1*B                              | GSTM1     | Anti-oxidative stress                                        | 229 recipients and 104 respective donors | British     | Lower risk of DGF in donors                     | [13]      |
| rs1695 genotype GG                   | GSTP1     | Anti-oxidative stress Anti-apoptotic                         | 223 controls and 273 recipients | North Indian | Higher risk of DGF                              | [14]      |
| rs1001179(-262C/T)                   | Catalase  | Anti-oxidative stress Anti-apoptotic Decrease toxicity of immunosuppressant | 187 recipients             | Polish      | Lower risk of DGF with T allele                 | [15]      |
| 242T allele                          | NADPH oxidase p22(phox) | Anti-oxidative stress | 196 donor-recipient pair | Iranian      | Higher risk of DGF in recipients                | [16]      |
| Telomere shortening                  | hTERT     | Telomere length: I/R and immunity Polymorphism limits telomere shortening | 119 kidney allografts      | Polish      | Lower risk of DGF                              | [17]      |
| rs2735940                            | Unknown (chr 18) | hTERT | Telomere length: I/R and immunity Polymorphism limits telomere shortening | 119 recipients | Polish      | Higher risk of DGF                              | [18]      |
| rs2735940                            | hTERT     | Telomere length: I/R and immunity Polymorphism limits telomere shortening | 74 donor-recipient pairs   | Polish      | Higher risk of DGF in recipients                | [19]      |
| Chemokines                           |           |                                                             |                            |             |                                                 |           |
| Genotype 1/2 (410/240) in intron 2   | IL-1Ra    | Inhibitor of IL-1 [inflammation and immunity] Genotype 1/2 leads to lower levels of IL-1Ra | 136 controls and recipients | Indian      | Higher risk of DGF                              | [20]      |
| -308G>A                              | TNF-α     | Pro-apoptosis                                                | 100 recipient-donor pairs | Iranian     | Higher risk of DGF with A allele in donors and lower risk with GG genotype in donors | [21]      |
| -1082G>A                             | IL-10     | Downregulation of inflammatory responses                    | 100 recipient-donor pairs | Iranian     | Higher risk of DGF with A allele when associated with A allele in TNF-α -308G>A in donors | [21]      |
| rs3732379 CC genotype                | CX3CRI    | Cell migration                                               | 270 recipients             | Caucasian   | Higher risk of DGF                              | [22]      |
| T-cell homeostasis                   |           |                                                             |                            |             |                                                 |           |
| rs231775 (+49A>G)                    | CTLA4     | Downregulation of T cell activation                          | 269 renal transplant recipients | Caucasian | Higher risk of DGF with G allele                | [23][24] |
| rs231775 (+49A>G), rs3087243 and 3’-UTR dinucleotide AT repeat |            |                                                             | 350 controls and 190 recipients | Indian      | Higher risk of DGF with G allele Lower risk of DGF with A allele Higher risk of DGF with 110-bp and 116-bp alleles Lower risk of DGF with 102-bp allele | [23][24] |
In their first publication in 2015, the authors showed that graft rs2735940 hTERT polymorphism was associated with a lower risk of DGF. rs2630578 BICD1 and rs7235755 chromosome 18 polymorphisms in the graft were associated with higher serum creatinine concentrations in the early period following KTx but not with DGF. These results suggest a negative correlation between the length of telomeres and I/R injury severity [17]. In 2016, the same authors reported that the presence of chromosome 18 rs7235755 polymorphism in recipients was associated with higher risk for DGF. Polymorphism in BICD1 in recipients was also associated with higher serum creatinine concentrations in long-term follow-up after KTx. Polymorphisms in hTERT were not associated with kidney allograft outcomes [18]. In 2017, Kłoda et al. [19] studied 74 Polish deceased donor and recipient pairs. Both donors’ and recipients’ rs2735940 hTERT TT genotypes were associated with DGF but not with AR. The rs2735940 hTERT TT donor genotype decreases the risk for DGF, while the rs2735940 hTERT TT recipient genotype increases the risk for DGF. DGF occurrence was five times higher for a CX (CT or CC) donor genotype and TT recipient genotype. rs2630578 BICD1 and rs7235755 chromosome 18 polymorphisms in recipients or donors were not associated with either DGF or AR [19]. The limitation of telomere shortening in donors, as observed in the case of rs2735940 hTERT polymorphism, is thus regarded as protective against renal I/R injury.

### Chemokines

**Regulation of the interleukin-1 pathway: interleukin receptor antagonist intron 2 polymorphism.** The interleukin (IL)-1 pathway is unique in having a natural inhibitor known as the IL-1 receptor antagonist (IL-1Ra). Manchanda et al. [20] studied 136 Indian KTRs from a related living donor and focused on three polymorphisms in the IL-1 gene cluster: IL-1β promoter region –511, IL-1β exon-5 and IL-1Ra in intron 2. Five alleles of the IL-1Ra have been reported, corresponding to 2, 3, 4, 5 and 6 copies of an 86-base pair repeat located in intron 2. Genotype 1/2 (410/240) of IL-1Ra was associated with a higher risk of DGF in this cohort. A homozygous state of allele 2 is a greater producer of IL-1Ra than the heterozygous or wild-type homozygous states. Therefore genotype 1/2 of IL-1Ra may be considered as a ‘low producer’ of IL-1Ra, which in turn cannot counteract the pro-inflammatory response of IL-1 at the time of renal I/R injury [20].

**Apoptosis and inflammation: tumour necrosis factor-α -308 G > A and IL-10 -1082 G > A polymorphisms.** Tumour necrosis factor-α (TNF-α) and IL-10 play a crucial role in the pathogenesis of renal I/R injury. Activated macrophages secrete TNF-α, which binds to TNF receptors on cells, leading them to apoptosis. IL-10 appears to limit and control inflammation [46]. Deletion of the IL-10 gene accelerates kidney graft AR in mice [47]. Mandegary et al. [21] enrolled a prospective single-centre cohort of 100 Iranian consecutive kidney recipient–donor pairs. Significant associations were found between donors’ TNF-α polymorphism -308G > A and the occurrence of DGF, as well as between the combination of donors’ IL10 AA or GA and TNF-α AA or GA genotypes and DGF [21]. McDaniel et al. [30] studied cytokine polymorphisms in 77 African American allograft recipients and 77 controls. TNF-α polymorphism in recipients was not associated with either DGF or AR [30]. Finally, Israni et al. [31] recruited 965 recipients of deceased donor kidneys from 512 donors. Recipient’s ethnicities included African American, White, Asian and Native American. Donor’s ethnicities were African American and White. Donor’s TNF-α polymorphism was not

| Polymorphism | Gene | Role of the molecule | Reference |
|--------------|------|----------------------|-----------|
| TLR3 F412L (rs3775291) | Pro-inflammation | Higher risk of DGF | [25] |
| rs10509681 (CYP2C8*3) | Biosynthesis of ETTs, which are protective against I/R injuries | Higher risk of DGF with a allele | [26] |
| rs7851696 | Activator of the complement system via the lectin pathway | Higher risk of DGF with T allele | [27] |
| rs2735940 | Activator of the complement system via the lectin pathway | Higher risk of DGF | [28] |
| Polymorphism | Gene | Role of the molecule | n donors versus recipients | Nationality | Reference |
|--------------|------|----------------------|---------------------------|-------------|-----------|
| **Cascade of the oxidative stress** | | | | | |
| GSTM1*A, GSTM1*B and GSTM1null phenotype | GSTM1 | Anti-oxidative stress | 229 recipients and 104 respective donors | British | [13] |
| GSTM1null + GSTT1null phenotype | GSTT1 | Anti-apoptotic | | | |
| GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D | GSTP1 | | | | |
| MnSOD aa14Ala and MnSOD aa14Val | MnSOD | | | | |
| **239 + 34A/C 47C/T** | | | | | |
| **Telomere shortening** | | | | | |
| rs2735940 | hTERT | Telomere length: I/R and immunity | 119 recipients | Polish | [18] |
| rs2630578 | BICD1 | Telomere length: I/R and immunity | 74 donor-recipient pairs | Polish | [19] |
| rs7235755 | Unknown (chr 18) | Telomere length: I/R and immunity | 74 donor-recipient pairs | Polish | [19] |
| **Chemokines** | | | | | |
| -308G>A, rs1800629 and rs3093662 | TNF-α | Inflammation | 77 controls and recipients 965 recipients and 512 donors 100 recipient-donor pairs | African American Recipients: African American, White, Asian and Native American. Donors: African American and White Iranian | [30] |
| -308G>A | | Pro-apoptosis | | | |
| -1082G>A, -819C>T and -592C>A | IL-10 | Downregulation of inflammatory responses | 77 controls and recipients 965 recipients and 512 donors 100 recipient-donor pairs | African American Recipients: African American, White, Asian and Native American. Donors: African American and White Iranian | [30] |
| rs3024498 and rs2222202 | | Anti-apoptosis | | | |
| -1082G>A | | | | | |
| -330 (T>G) | IL-2 | Immunity and inflammation | 77 controls and recipients 965 recipients and 512 donors | African American | [30] |
| +869 T>C and +915 G>C | TGF-β1 | Inflammation and apoptosis | 77 controls and recipients 965 recipients and 512 donors | African American Recipients: African American, White, Asian and Native American. Donors: African American and White | [30] |
| rs1800472 and rs1982073 | | | | | |

(continued)
| Polymorphism                                                                 | Gene            | Role of the molecule                                                                 | n donors versus recipients | Nationality | Reference |
|-----------------------------------------------------------------------------|-----------------|--------------------------------------------------------------------------------------|----------------------------|-------------|-----------|
| -174, a (C>G)                                                               | IL-6            | Pro-inflammation and apoptosis                                                        | 77 controls and recipients | African American | [30]      |
| +874 (CA)                                                                   | IFN-γ           | Pro-inflammation and apoptosis                                                        | 77 controls and recipients | African American | [30]      |
| FYB null genotype or FYB null alleles and polymorphism at position 535     | DARC            | DARC binds to chemokines and reduces their level. Limitation of systemic inflammation | 222 recipients             | African American | [32]      |
| -511 (promoter region) and exon-5                                           | IL-1β           | Pro-inflammation                                                                     | 136 controls and recipients | Indian       | [20]      |
| IL12B 3’UTR                                                                 | IL-12p40        | Stimulating IFN-γ production                                                          | 253 recipients             | Caucasian    | [33]      |
| CCR2-V64I                                                                   | CCR2            | Receptors of chemokines, which play a role in infiltration and activation of macrophages | 100 donor-recipient pairs  | Iranian      | [34]      |
| CCR5-Delta32                                                                | CCR5            |                                                                                      |                            |             |           |
| rs6822844                                                                   | IL2-IL21 cluster| Regulation of T cells and NK cell functions                                          | 270 recipients             | Caucasian    | [35]      |
| 1188A>C                                                                     | IL-12B          |                                                                                      | 267 recipients             | Caucasian    | [36]      |
| -295T>C                                                                    | IL-16           | Pro-inflammation                                                                     |                            |             |           |
| 607C>A and 137G>C                                                           | IL-18           |                                                                                        |                            |             |           |
| Apoptosis                                                                   | TP53            | Pro-apoptosis                                                                        | 965 recipients and 512 donors | Recipients: African American, White, Asian and Native American. Donors: African American and White | [31]      |
| (GT)_n repeat                                                                | HMOX1           | Anti-apoptosis                                                                        | 965 recipients and 512 donors | Recipients: African American, White, Asian and Native American. Donors: African American and White | [31]      |
| Regulation of the innate and adaptive immune responses                       | PTPN22          | Negative regulation of T-cell reaction, negative regulatory kinase Csk and other signalling molecules | 269 recipients             | Caucasian    | [2]       |
| rs2476601                                                                   |                 |                                                                                        |                            |             |           |
| rs5742909                                                                   | CTLA4           | Downregulation of T cells activation                                                 | 350 controls and 190 recipients | Caucasian    | [23]      |
| rs11571317, rs16840252, rs4553808, rs3087243                                |                 |                                                                                        |                            |             |           |

(continued)
Table 2. Continued

| Polymorphism | Gene | Role of the molecule | n donors versus recipients | Nationality | Reference |
|--------------|------|----------------------|---------------------------|-------------|-----------|
| rs7574865    | STAT4| Regulation of natural killer cells, CD8<sup>+</sup> T cells and Th1 function Differentiation of B cells and regulatory T cells | 270 recipients | Polish | [37] |
|              |      |                      |                           |             |           |
| Regulation of the innate immune responses |      |                      |                           |             |           |
| R753Q (rs5743708) and R677W (del -196/-174) T737S (rs5743318) | TLR2 | Pro-inflammation | 265 recipients | German | [25] |
| D299G (rs4986790) and T399I (rs4986791) | TLR3 |                      |                           |             |           |
| 392STOP (rs5744168) | TLR4 |                      |                           |             |           |
| P545P (rs352140) and -1237T/C (rs5743836) -159C/T (rs2569190) | TLR5 |                      |                           |             |           |
| rs5498 rs1041163 and rs3170794 | CD14 |                      |                           |             |           |
| Metabolization of anti-inflammatory molecules rs890293 (CYP2J2)<sup>+</sup> | CYP2J2 | Biosynthesis of EETs, which are protective against I/R injury | 166 recipients | Caucasian | [26] |
| Complement rs11003125, rs7096206, rs7095891, rs5030737, rs1800450 and rs1800451 | MBL2 | Immunity and inflammation | 1271 donor-recipient pairs | Netherlands | [38] |
| rs72550870 | MASP2 |                      |                           |             |           |
| C3F | Complement C3 | Immunity and inflammation | 1265 donor-recipient pairs | Netherlands | [39] |
| rs17549193 and rs4521835 | FCN2 | Immunity and inflammation | 270 recipients | Caucasian | [27] |
| rs3124952, rs3124953, rs17514136, rs17549193 and rs7851696 |          |                      |                           |             |           |
| NO pathway G894T substitution within exon 7 | eNOS | Recovery of blood flow after ischaemia May reduce oxidative stress | 187 recipients | Polish | [28] |
| rs10918594 | NOS1AP | No pathway | 75 recipients | Polish | [40] |
statistically associated with DGF, although a positive trend was observed [31].

Cell migration: CX3CR1 V249I polymorphism. Fractalkine, also known as CX3CL1, is a member of the chemokine family that acts as an adhesion molecule and as an extracellular chemotactic promoting cell migration [48]. Dabrowska-Zamojcin et al. [22] enrolled 270 Caucasian KTRs to study the impact of polymorphism V249I (rs3732379) in the Fractalkine receptor gene, CX3CR1. This polymorphism has been associated with a reduced number of CX3CL1 binding sites, reduced cell adhesion and decreased signalling and chemotaxis. The rs3732379 CC genotype in KTRs was associated with an increased risk for DGF [22].

T-cell homeostasis (CTLA-4 pathway)
Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is expressed at the surface of activated CD8 and CD4 T cells. It plays an inhibitory role in inflammation and helps maintain peripheral tolerance by suppressing T-cell proliferation and by inducing apoptosis of activated T-cells [24]. Doan et al. et al. [23] enrolled 269 Caucasian KTRs to study the impact of rs231775 (+49 A>G) polymorphism in CTLA4 and found an association with the G allele in rs231775 and a higher risk of DGF [23]. Similarly, Misra et al. [24] enrolled 350 Indian patients with end-stage renal disease (ESRD) and 350 controls. Among the 350 ESRD patients, 190 underwent KTxs. The CTLA-4 variants rs231775, rs3087243 and 3′-UTR dinucleotide AT repeats in recipients were involved in genetic susceptibility to DGF. The A allele in both rs231775 (+49 A>G) and rs3087243 was considered as protective against DGF, while the G allele was associated with a higher risk of DGF. Concerning 3′-UTR dinucleotide AT repeats, the 102-bp allele was protective against DGF, while 110-bp and 116-bp alleles increased the risk for DGF [24].

Regulation of the immune response
The toll-like receptor (TLR) system is key in the innate immune system and participates in both acute and chronic allograft dysfunction [25, 49]. Loss-of-function mutations of TLR4 in donors have been associated with improved immediate kidney allograft outcomes [50]. Therefore, Krüger et al. [25] hypothesized that genetic variations in the TLR system may affect clinical outcome after KTxs, including DGF. They enrolled 265 German KTxs to evaluate the impact of selected polymorphisms in the TLR2, TLR4, TLR5, TLR9 and CD14 genes. The study showed that the TLR3 F412L polymorphism had a significantly higher rate of DGF in a univariate analysis but was not statistically significant after adjusting for known risk factors of DGF. Every other polymorphism tested had no significant association with DGF [25].

Epoxieicosatrienoic acids (EETs) are vasodilatory factors with anti-inflammatory properties. They may play a protective role against I/R-related damage [51, 52]. Several cytochrome P450 (CYP450) isozymes mediate the biosynthesis of EETs [53]. In humans, CYP2J2 and CYP2C8 are the most important isozymes. CYP2J2*7 (rs890293) and CYP2C8*3 (rs10509681) are the most common variants affecting enzymatic activity in Caucasians [26]. Gervasini et al. [26] studied these polymorphisms in 166 consecutive Caucasian adult KTxs. CYP2C8*3, which caused decreased enzymatic activity and lower production of EETs, was associated with a higher incidence of DGF in this cohort [26].

Ficolin (FCN)-2 is an activator of the complement system via the lectin pathway. Complement activation plays a substantial role in I/R injury at the time of KTxs [27, 39]. The FCN-2 rs7851696 T allele is known to be associated with increased affinity of lectin-2 for carbohydrate structures presented by different pathogens [54]. Dahle et al. et al. [27] enrolled 270 Caucasian deceased-donor KTxs to evaluate the impact of FCN-2 gene rs7851696, rs17549193 and rs4521835 polymorphisms in DGF, as well as in AR and chronic allograft dysfunction. The results showed an increased risk for DGF and AR in case of FCN-2 rs7851696 T allele, although these statistical associations were not significant after Bonferroni correction [27].

Finally, nitric oxide (NO) plays a critical role in vascular tone and host defence [40, 28]. There are two distinct forms of NO synthases (NOSs): constitutive endothelial NO (eNOS) and inducible NO (iNOS). eNOS helps in tissue reperfusion and recovery after ischaemia and may reduce oxidative stress [28]. Dutkiewicz et al. [28] enrolled 187 polish KTxs to study the impact of polymorphisms of the eNOS gene (G894T substitution within exon 7 and intron 4 VNTR) on DGF, AR and chronic rejection and found an association between the a allele of the eNOS intron 4 VNTR polymorphism and a higher risk for DGF [28].

DISCUSSION
Among 30 studies in the literature, 16 reports suggest an association between polymorphisms and the occurrence of DGF (Table 1), whereas 14 papers failed to find any relationship (Table 2). As discussed below, it is interesting to note that genes implicated in similar I/R-related pathways may or may not be involved in genetic susceptibility to DGF. Hence several genes connected to oxidative stress have been studied. I/R-related ROS cause deleterious effects on kidney allografts by triggering inflammatory injuries [13, 14]. High-producer polymorphisms in genes coding for antioxidant proteins have been associated with a lower risk of DGF, such as the presence of the -262 T allele in the KTR CATALASE gene [15] or the presence of the B allele in GSTM1 (GSTM1*B) in kidney donors [13]. In contrast, low-producer polymorphisms have been shown to be deleterious in I/R injury, including rs1695 genotype GG in GSTP1 in KTxs [14]. Furthermore, high-producer polymorphisms in genes coding for pro-oxidant proteins have been associated with a higher risk of DGF, like NADPH oxidase p22(phox) 242 T allele (CT + TT) in KTxs [16]. Still, other reports focusing on the oxidative cascade failed to link gene polymorphisms and DGF. As an example, 239 + 34 A/C and 47 C/T polymorphisms in the SOD1 and SOD2 genes were not associated with DGF development (Table 2) [29]. Superoxide dismutases (SODs) are regarded as the most important enzymes against ROS, particularly against superoxide anion radicals.

Kidney aging may be notably reflected by telomere length [17, 19, 55], and in the case of KTxs, assessment of telomere length in the early post-transplant period allows prediction of allograft long-term outcomes [56]. In case of renal graft I/R, a significant decrease in telomere length has been reported, thus suggesting accelerated kidney senescence [17, 44]. Conversely, limitation of telomere shortening in recipients may favour the deleterious immune response [45]. Hence polymorphisms rs2735940 hTERT (leading to limited telomere shortening) in donors was associated with a lower risk for DGF [17, 19]. However, this very same genotype in recipients was associated with increased risk for DGF, most probably due to an amplified immune trigger [19]. Such a condition exemplifies the importance of distinguishing the donor from the recipient genotype at the time of studying genetic susceptibility to renal I/R. Polymorphisms involved in I/R severity may be particularly
The pathophysiology of DGF is complex and multifactorial, including immunological and non-immunological factors [8, 7]. Furthermore, there might be additive actions of both I/R and AR in the immediate post-transplant period, which may synergistically predispose to DGF. The actual role of genetic susceptibility to renal I/R may thus be difficult to appropriately ‘quantify’ [30].

Genome-wide association studies (GWASs) are currently ongoing to test additional genes and SNPs in the particular settings of DGF. Confirmatory clinical trials are also required in validation cohorts. As an example, two SNPs (rs3811321 and rs6565887 on chromosomes 14 and 18, respectively) have been initially identified by GWASs in 300 KTRs as predictive of serum creatinine levels and hard clinical outcomes. However, Pihlstrøm et al. [59] failed to confirm such an association between these two polymorphisms and post-transplant outcomes in 1638 recipients. Indeed, conflicting data may result from the number of recruited patients and from their ethnicity. Polymorphisms in the TNF-α gene in 100 Iranian donors were associated with DGF occurrence [21] but failed to be confirmed in a large cohort including 512 African American and White donors [31].

African American recipients have shown a higher risk of DGF [60, 61]. Black ethnicity in recipients is a risk factor for DGF [62], which is part of the nomogram established by Irish et al. [63] for predicting the likelihood of DGF. Nevertheless, Palanisamy et al. [61] showed that cardiovascular risk factors contribute to disparities in graft outcomes in African American KTRs. Furthermore, after correcting for cardiovascular risk factors, race per se did not show an independent effect on graft outcomes [61].

In conclusion, several polymorphisms in either the donor or the recipient or both have been associated with DGF in KTRs. These polymorphisms are involved in oxidative stress, telomere length, cytokine secretion and modulation, immunity and inflammation. These processes are involved in I/R injury, which is regarded as one of the most important causes of DGF. Identifying the polymorphisms linked to renal I/R may allow us to better understand its pathophysiology and find new therapeutic targets.

The present review highlights the state of knowledge in the field of genetic susceptibility to renal I/R. Although SNPs may only have minor impacts per se on gene expression and protein function, interactions among multiple SNPs may have a major impact on molecular cascades [39]. Additionally, some SNPs show very low frequency [31]. Validation studies are lacking or inadequately powered for most SNPs studied thus far [39], which may explain the controversial observations [21, 31]. Replication studies will need to include multivariate analyses to isolate the putative effects of SNPs among other well-established risk factors of DGF. Most importantly, one must clearly distinguish the impact of SNPs in donors versus in recipients versus in both. Polymorphisms involved in I/R severity may be particularly relevant in donors, whereas polymorphisms implicated in AR and inflammation may rather concern recipients [19]. Therefore, prospective multicentric studies including patients of various genetic backgrounds are required to clinically determine the benefits (and harms) of genotypeing donors and recipients before KTx [59, 12].

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**AUTHORS’ CONTRIBUTIONS**

J.H. performed the original research of the literature and wrote the article. J.-M.K. wrote the article. F.J. supervised the original research of the literature and wrote the article.

**CONFLICT OF INTEREST STATEMENT**

The authors declare no conflict of interest.

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