SECTION 4

Exposures and Patient Susceptibility

CHAPTER 15

Genetic Predisposition for Acute Kidney Injury (AKI)

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OBJECTIVES

This chapter will:

1. Describe the strategies used for looking at single nucleotide polymorphisms associated with acute kidney injury traits.
2. Review the main studies reporting associations between genes of interests and acute kidney injury traits.
3. Propose to develop "agnostic" genome-wide associations to discover potential pathways involved in acute kidney injury.

BACKGROUND

Genetic Approaches

The field of genetic implication on many diseases results from studies of Mendelian traits, in which typically there was a one-to-one relationship between a mutation and a phenotype.[1] Diagnostic and prognostic values of identifying such mutation are strongly related. In contrast, genetic studies for more complex diseases, *a fortiori* for syndromes as acute kidney injury (AKI), have looked at genetic variants associated to occurrence, severity, or outcome of these syndromes. Prevalence of variants differs only slightly between persons with a given syndrome or disease and those without it, having then little or no predictive utility. This apparent limitation for using genetic tests may be seen as irrelevant for the studied syndrome. However, it may represent therapeutic targets for potential interventions on gene-associated biologic pathways. For the vast majority of variants associated with complex disease, we have no understanding of the biologic processes and pathways involved in disease causation; this is an important problem. Moreover, little is known about the function of the majority of genes in the genome. As a consequence, we have no way of knowing whether the causal variant increases or decreases gene expression, modifies protein interactions or localization, or changes their activity.

The development of large-scale studies using genome-wide associations (GWAs) sounds adequate, because this method has a high resolution for single nucleotide polymorphism (SNP) detection, is an "agnostic" evaluation, can be related to any trait, and may provide signals in previously unsuspected genes or gene "desert." The rapid advances in technology and quality control permit reliable genotyping of up to 1 million SNPs in a single sample of an individual.[1] Only a few GWAs have been performed in nephrology, and none has been performed on AKI in intensive care patients. One example applying the GWAs method for kidney disease was reported in 2011, looking at SNPs associated with the biopsy-proven diagnosis of idiopathic membranous nephropathy.[2] Among investigated SNPs, only one (HLA-DQA1 allele in chromosome 6p21) was associated closely with this glomerulopathy in person with white ancestry.

Association With Candidate Genes

Another approach is based on association of candidate genes identified in several ways. Most are suggested by studies of immune mechanisms in infectious diseases, such as major histocompatibility (MHC) genes and cytokine and chemokine genes and their receptors. This chapter reports mainly such studies but with the limits of these studies to interpret the results from literature.[3] This is complicated by apparent inconsistencies between different populations for any associations primarily because of poor study design. The small number of patients with lack of power to detect convincing allelic associations with odds ratios less than 2 or greater than 0.5 are the main causes for the limited validity of these studies. Performing sequential studies, using the results from the first raising a small number of specific hypotheses for testing in the second, is an efficient means to deal with extensive allelic diversity. The adequately

matching control group to the cases is another difficult problem to resolve, especially in large urban cities. The limits of such approach are the following[3]:

1. The limitation of SNP association with genes supposed to control pathways known to play a role in the complex disease
2. The impossibility to discover new genes/pathways that had never been described in such diseases
3. The lower resolution than the one obtained with GWAs method
4. The poor reproducibility according to the patient's selection, the cohort size, and the traduction in potential therapies

Genetic Variability and Acute Kidney Injury

The evaluation of potential contribution of genetic variability on occurrence, course, and severity of AKI sounds like a reasonable approach, because patients facing similar injury conditions may or may not develop an AKI, even after controlling the confounding factors such as comorbidity.[3] In absence of any GWAs on AKI population, only studies about association between preselected polymorphism(s) and AKI have been reported.[3,4] As mentioned above, some limitations impede the validity of the results: limited size of the investigated cohorts, heterogeneity between patients because of different medical context, AKI definition, and supportive therapies, especially renal replacement therapy (RRT). The *a priori* determination of association between SNPs of genes of interest and AKI had restricted the investigation to several pathways known for their implication in AKI mechanisms. Among these mechanisms, inflammation, metabolism, control of renal vascular tone, and reactive oxygen species production or their "detoxifying" routes were reported most frequently.[3,5] This chapter summarizes the main results of SNPs associated with AKI, grouping results of recent reviews testing the quality control of the published results and more recent individual articles.[3,4]

DIFFICULTIES IN DEFINING THE GENES OF INTEREST IN ACUTE KIDNEY INJURY

Because AKI is a syndrome and not a disease, it is tempting to group the accepted arguments for AKI mechanisms to better define the genes of interest.[5] Because the leading clinical conditions associated with AKI (sepsis, major surgery, heart failure, and severe hypovolemia) frequently are associated with the presence of shock, it seems logical to attribute AKI to renal hypoperfusion/ischemia in presence of hypotension and/or low systemic blood flow.[5] However, sepsis-induced AKI was shown to be associated rarely with decreased RBF states,[6] with a concomitant elevated cardiac output after fluid challenge resuscitation and/or pressors infusion to maintain blood pressure.[7,8] AKI may occur in the absence of overt signs of hypoperfusion or shock or in absence of macrohemodynamic signs of hypoperfusion. This observation prompts to consider other mechanisms than renal hemodynamic impairment, such as inflammation, alteration of microvascular flow at the peritubular and glomerular levels, alteration of mitochondrial function, and cell cycle arrest.[5] This statement is supported strongly by the observations made on renal biopsies performed early after patient death in a context of severe sepsis or septic shock.[9] These biopsies showed important infiltration by monocytes and poly morpho nuclear cells (PMNs) with a high rate of apoptotic cells. Surprisingly, relatively few lesions related to renal ischemia could be described.[9] The selection of genes of interest for potential susceptibility to AKI then may be linked to the main pathways fitting to these observations. The selection of the clinical traits to be tested in terms of SNPs association is an important step. It could be the prediction of the risk of AKI, the risk of severe AKI, or the outcome of AKI patients. Some reviews have reported the results published from 1950 until 2014 on polymorphisms associated with AKI[4] or from 2000 to 2014.[3]

GENES ASSOCIATED WITH ACUTE KIDNEY INJURY

Mechanistic Approach to Select Gene Associations

The combination of acute insults and comorbidities renders complex and hazardous the demonstration of associated genetic polymorphisms supporting the concept of individual susceptibility to AKI. In consideration of the cell compartments of the normal renal tissue, potential susceptibility may concern epithelial cells, endothelial cells, and resident immune cells. In stress conditions with systemic inflammation, the immune cell compartment may largely change,[10] as observed in renal biopsies.[9] One important acceptable hypothesis is to consider the blood milieu as a "good biopsy" for renal inflammation markers, cell activation, transcriptome, and genotyping guiding the selection of genes of interest. In 2009 Lu et al.[11] performed a systematic review of genes that influence AKI covering the period from 1950 to 2007. They found 16 studies on cohort or case-cohort investigating 35 SNPs in 21 genes associated with AKI. The studied populations were primarily critically ill premature infants or adults or postcardiac surgery patients. At this time, five different definitions of AKI have been used, an important confounding factor for analysis. Among the reported SNPs, only one polymorphism (APO E e2/e3/e4) was present in more than one study showing a significant impact on AKI incidence.[11] The mean quality score was low, studies were heterogeneous, and the scarcity of studies precluded additional meta-analysis of the results. They concluded that "current association studies are unable to provide definitive evidence linking genetic variation to AKI. Future success will require a narrow consensus definition of AKI, rigorous epidemiologic techniques, and a shift from *a priori* hypothesis-driven to genome-wide association studies."[11]

Investigated Gene Associations With Acute Kidney Injury

Inflammatory Genes

If the consensus definition of the AKI goal has been achieved,[12] there were no reported GWAs studies on AKI. More recently, another review on systematic literature focused on genetic predisposition to AKI or outcome was published.[3] The researchers searched in databases covering the period between 2000 and 2015 and followed the recommendations of the Human Genome Epidemiology Network. Among the 4027 selected articles with interest in genetic variability in AKI, only 37 articles were selected, keeping only 28 articles after removing those published

in abstract form only. These articles were heterogeneous with a moderate quality (mean 6.4 of 10). The authors concluded, "Despite different gene polymorphisms with suggested associations with development or severity or outcome of AKI, definitive conclusions would require replication of associations in independent cohort studies and, preferably a hypothesis-free study design."[3] Details of the main findings of this review are presented in the chapter, with more recent publications genes polymorphism positively or negatively related with susceptibility to AKI or outcome. For inflammatory genes, the *a priori* selected genes focused on tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), and IL-6 cytokines release. Studies performed in adult patients having cardiopulmonary bypass surgery showed that association between IL-6 gene -572G/C polymorphism or IL-10 gene -592 C/A polymorphism and AKI was not confirmed by subsequent studies.[13] In a study performed in similar patients, a combination of angiotensinogen (AGT) gene +842C –allele and IL-6–572C –allele was associated with renal dysfunction.[14] The most frequently investigated polymorphism concerned the classic TNFα-308 G/A polymorphism.

Jaber et al.[15] have evaluated single nucleotide polymorphisms in the promoter region of TNF-α and IL-10 in a cohort of 61 patients with acute renal failure requiring intermittent hemodialysis. Although the patients were not well described, 43% died with for 65% in a context of multiple organ failure. In the survivals, 69% recovered a normal renal function. They explored the relationship of these polymorphisms to clinical outcomes as mortality and recovery of renal function. Compared to genotype frequencies from control subjects (from literature), TNF-α high-producer genotypes and IL-10 low producers were more prevalent in the study cohort. Interestingly, performing ex vivo endotoxin-stimulated white cells, TNF-α, and IL-10 were shown higher in patients with high-producer genotype for TNF and for IL-10, even after adjustment for white blood cell count. TNF-α high-producer genotypes were associated with high Acute Physiology and Chronic Health Evaluation (APACHE) score values and were related to high risk of death after adjustment on APACHE level and for the presence of sepsis or not. IL-10 genotype, on the contrary, was not associated with mortality. The genetic combinations showed 78% of survival when low-producer TNF-α and IL-10 genes were present and was only 45% in both high-producer genotypes. The authors concluded that "cytokine gene polymorphisms essentially predict outcome in patients with acute renal failure (ARF) requiring renal replacement therapy (RRT)." Mortality in the ARF group was higher in patients with the mutation -308 G→A polymorphism for the promoter region of TNF-α gene, associated with high levels of TNF-α and the -1082 G→A polymorphism of the promoter region of IL-10 gene associated with a lower levels of IL-10 production. Dalboni et al.[16] have tested in 303 ICU patients and 244 healthy individuals if the TNF-α-308 G/A, IL-6 -174G/C, and IL-10 -1082 G/A polymorphisms may predispose to the development of AKI or death. The group of patients who developed AKI (n = 139) had a significantly lower incidence of TNF-α -308 GG (low-producer phenotype) than in the group of patients without AKI or in healthy individuals. Grouping the combinations of the tested polymorphisms, the authors observed that the combination of low TNF-α + low IL-10 producer phenotypes was an independent risk factor to AKI and/or death and RRT in ICU patients.

In 2014 the same group reported a study performed on an extended cohort of similar patients investigating polymorphism for TGF-β and IFN-γ. They tested whether the genetic polymorphisms of TGF-β codon 10 T/C and codon 25 C/G and IFN-γ +874 T/A may be a risk factor for ICU patients to the develop AKI and/or to die. In the studied population, the polymorphism of TGF-β and IFN-γ was not associated as a risk factor for AKI or death. In 2012 Payen et al. reported the association between AKI severity and outcome and the genotyping of 13 HLA-DRB1 alleles.[20] The major complex of histocompatibility class II (MHC II) is key for the "synapse" between innate and adaptive immunity.[17] It is well evaluated in antigen-presenting cell membranes by the surface expression of HLA-DR.[18] In addition, HLA-DR is expressed constitutively in peritubular and glomerular capillary endothelium,[19] a unique organ property that may contribute to the kidney response to foreign antigens. Among the mosaic of MHC class II genes, HLA-DRB genes are highly polymorphic and were chosen to detect a haplotype-phenotype association with a greater probability. This expression was measured in 176 multicentric adult patients in severe sepsis and septic shock.[20] The genotyping concerned 13 alleles of HLA-DRB1. The presence of at least four HLA-DRB1 alleles or more appeared protective for severe AKI, with a significantly lower (58%) proportion in patients with severe AKI requiring RRT than in those having severe AKI without RRT (84%).

As mentioned above, the infiltration of the kidney at the acute phase of sepsis by inflammatory cells seems clear[21] and may be a key mechanism for tubular cells' functional impairment.[5] Such a concept was verified by in 2016 by Chousterman et al.[21] using a mouse model of AKI and human data. The observed adhesion of the monocyte on renal vascular wall depends on intensity of the expression of a chemokine receptor CX3CR1, which may then modulate the extent of kidney lesions. These lesions were shown reduced when CX3CR1 activity increased in several conditions such as coronary artery disease[22] or neuroglioblastome[23] and others. As part of the paper, the search for a polymorphism for gene controlling CX3CR1 activity was investigated in a multicentric cohort of 239 severe septic or septic shock patients. The CX3CR1 polymorphism (VV genotype of VI genotype) tested the allele I249 versus V249. In vitro adherence of peripheral blood monocyte from healthy donors heterozygous for the I249 allele were significantly more frequent than those homozygous for V249 allele. The I249 allele then was tested in the cohort of 239 septic patients. The I249 allele was present in nearly 50% of the patients and was associated with a lower incidence of AKI after elimination of confounding factors, with an odds ratio of 0.43. This result showed that the I249 allele of CX3R1 is associated with a reduced AKI incidence in septic patients, probably related to the protective effect of CX3CR1 activity.

Genes Regulating the Vasomotor Tone

Because hemodynamic and inflammatory mechanisms are intricate, looking at polymorphisms for pathways participating in the control of vascular tone is reasonable. Six studies have investigated angiotensin-converting enzyme (ACE) insertion/deletion polymorphism.[3] Four studies failed to detect association with increased risk of AKI and necessity for RRT in ICU patients or after cardiac surgery. The two remaining studies provided contradictory results.[24,25] Only one study has shown an association between the ACE D-allele and an increased risk of postoperative AKI after cardiac surgery.[24] It becomes difficult to draw any conclusion about a true association between ACE polymorphism and risk of AKI.

Similarly, polymorphism within catechol-o-methyl transferase (COMT) gene and AKI was negative for two

studies.[26,27] Because of the crucial role of nitric oxide (NO) in vasomotor regulation especially at the renal vasculature,[28] eNOS polymorphism associated with renal dysfunction is a reasonable hypothesis. Popov et al.[29] have looked at the eNOS T-786C polymorphism in 497 patients undergoing cardiac surgery with cardiopulmonary bypass. This eNOS polymorphism, one of the most important for the regulation of the transcription rate of the eNOS gene, has been shown to be associated with various cardiovascular diseases. It has been reported that the presence of the C allele induces a significant lower promoter activity compared to the T allele, which is consistent with reduced NO production. Patients were grouped on the basis of whether they were homozygous or heterozygous for the C allele (TC + CC) or only homozygous for the T alleles (TT). TC + CC alleles were associated with a significant minimal creatinine clearance lower than in TT allele group, and a higher proportion of RRT during hospital stay.

Other Gene Polymorphisms

Metabolic pathways participating in immune cellular function capabilities may be seen as a potential modulator of inflammation.[30,31] The association between renal function alteration and polymorphism of key enzymes or major factors has been investigated. In 2000 Chew et al.[32] tested in 564 coronary bypass patients the hypothesis that apolipoprotein E alleles could be associated with different postoperative changes in serum creatinine after cardiac surgery. Renal function was assessed by comparison between preoperative, perioperative, and peak postoperative serum creatinine levels. Inheritance of the apolipoprotein E4 allele was associated with reduced postoperative increase in serum creatinine after cardiac surgery, compared with the e3 or e2 alleles, which raises questions regarding apolipoprotein E role in AKI. These associations have not been confirmed by other studies.

Only one study found a polymorphism in the pro-oxidant enzyme *NADPH* (nicotinamide adenosine dinucleotide phosphate) *oxidase p22phox*,[33] a key enzyme for oxidative stress-mediated injury. The polymorphism +242 C/T and on the promoter -262 of the antioxidant enzyme catalase gene in a cohort of 200 hospitalized patients for established acute renal failure of mixed cause and severity were investigated. Genotype associations were characterized by measuring plasma level of nitrotyrosine and catalase activity. A genotype–phenotype association was demonstrable between the *NADPH oxidase p22phox* genotypes and plasma nitrotyrosine level, as well as between the *catalase* genotypes and whole-blood catalase activity. Compared with the *NADPH oxidase p22phox CC* genotype, the T-allele carrier state was associated with 2.1-fold higher odds for dialysis requirement or hospital death, even after adjustment on confounding factors.

FUTURE DIRECTIONS: GENOME-WIDE ASSOCIATIONS

Most of the quoted studies have been considered to have an inadequate quality (mean score 6.4/10) with heterogeneity in defining concepts and outcomes, being underpowered and replicated with ambiguous results. Studies looking at inflammatory pathways are the most frequently reported investigation with poorly replicated studies. The choice of relevant genes for association with AKI in hemodynamic contexts was mostly those that participate in vasomotor tone control. The results appear poorly contributive and confusing, with almost no confirmation for associations. If the sample size and the internal replication are the most important criteria for quality, large cohorts have to be grouped and replicated from a new set of similar patients. In the near future, whole gene(s) should be covered instead of genotyping some random SNPs. Such a goal will be achieved using the GWAs method for *non a priori* studies using a high-flux sequencing method. The example using GWAs to explore SNPs association with idiopathic membranous nephropathy diagnosis,[2] was performed in 556 patients originating from three populations. A large fraction of these patients were used to find SNP associations, which were tested in the remaining patients. The observed significant association with HLA-DQA1 polymorphism with high odds ratio when homozygosity was present provides a credible result about facilitation of an autoimmune response against targets.

In 2010 a meta-analysis of GWAs in 67,093 individuals from 20 population-based studies was published.[34] The aim was to identify new susceptibility loci for reduced renal function (creatinine level or creatinine clearance). After replication of 22,982 samples, 13 new loci affecting renal function and 7 loci suspected to affect creatinine production and secretion were identified. These results potentially influence nephrogenesis, podocyte function, angiogenesis, solute transport, and metabolic functions of the kidney. Such approach is warranted for AKI in intensive care patients.

Key Points

1. Genetic susceptibility for acute kidney is reasonable because, while facing similar stress conditions, some patients experience an acute kidney injury (AKI) and others do not.
2. Genetic involvement may only concern associations of single nucleotide polymorphisms with clinical traits, being out of a pure Mendelian genetic (one mutation-one phenotype).
3. Strategy for single nucleotide polymorphisms had been driven primarily by recognized pathways participating in AKI mechanisms, which implies a reduced chance to discover new pathways.
4. The future to assess a genetic susceptibility may come from screening a large number of genes as a blinded research, using the genome-wide association method.
5. Until now, the small number of patients, the limited quality of the clinical studies, and their heterogeneity preclude any conclusion on a potential genetic role for AKI occurrence, severity, and recovery.

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A complete reference list can be found online at ExpertConsult.com.

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