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Susceptibility genes in common complex kidney disease

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Abstract

Purpose of review—This manuscript reviews recent efforts to identify genetic variants conferring risk for chronic kidney disease (CKD). A brief overview of methods for identifying gene variants is provided, along with genetic associations and new avenues under exploration.

Recent findings—The role of renal failure susceptibility genes including *MYH9*, *ELMO1*, *UMOD* and *ACTN4* has become clearer over the last 18 months. The spectrum of *MYH9*-associated kidney disease including focal segmental glomerulosclerosis (FSGS), global glomerulosclerosis and collapsing glomerulopathy, related entities contributing to approximately 43% of end-stage renal disease in African Americans, has come to light.

Summary—*MYH9* will re-categorize FSGS and related disorders, and has clarified the relationship between hypertension and kidney disease. *MYH9* polymorphisms account for much of the excess risk of HIV-associated nephropathy and non-diabetic kidney disease in African Americans. Kidney disease associations with *ELMO1* and *UMOD* have been replicated and applications of genome-wide association studies based on expression data are providing novel insights on renal protein expression. These breakthroughs will alter our approach to kidney disease surveillance and lead to new therapeutic options.

Keywords

diabetes mellitus; ELMO1; focal segmental glomerulosclerosis; genetics; kidney disease; MYH9

Introduction

Improvements in genotyping, computing and statistical analysis now make it possible to scan the entire genome using single-nucleotide polymorphisms (SNPs) and apply novel methods such as mapping by admixture linkage disequilibrium (MALD) and genome-wide association study (GWAS) to detect chronic kidney disease (CKD) genes. This paper reviews newer genetic methodologies and recently detected genes causing focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, global glomerulosclerosis (historically labeled “hypertensive nephrosclerosis”) and diabetes-associated nephropathy. These findings will

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allow for pre-symptomatic disease screening and potentially intervention in novel pathways to prevent or slow progression to end-stage renal disease (ESRD).

1. Approaches to identifying nephropathy genes

Linkage analysis systematically scans the genome of affected individuals in families using highly polymorphic markers (microsatellite repeat polymorphisms or SNPs) with known genomic positions [1]. Linkage relies on the fact that the shorter the distance between genetic variants the more likely they are to be co-inherited. Genetic regions harboring nephropathy risk variants can be identified by observing that affected family members tend to share the same marker variants (alleles) in the same genomic region more frequently than expected by chance. Families are often limited to sibling pairs or two-generations due to the late age at nephropathy onset, thus requiring greater number of families than would be the case for early onset diseases. Linkage studies are difficult and expensive due to the need to recruit large numbers of informative families. Moreover, linkage has poor resolution requiring additional efforts to refine locations of disease variants using genetic association studies (GAS).

GAS can detect genetic variants either associated with the trait of interest or in linkage disequilibrium with an untyped variant. This approach can detect smaller effect sizes than what is feasible with linkage analysis. However, association studies in unrelated individuals are vulnerable to confounding by population stratification or admixture and even after controlling for these effects; identification of causative genes still depends on the presence of relatively common risk allele frequencies [2-5].

It is now possible to perform association analyses using upwards of 1 million SNP markers. From a methodologic standpoint, GWAS are no different than traditional GAS; except the sheer amount of data creates computational challenges and raises additional statistical concerns. For example, special software to manipulate the collected data and conduct the analysis had to be developed [6;7], and the effect of statistical effects such as the “winner's curse” are magnified [8].

MALD is the first post-linkage methodology that interrogates the whole genome for disease association. It relies on the premise that if the prevalence of a disease is higher in one ancestral population than another, it will be easier to identify causative variants in the admixed population than in either parental population alone [9;10]. African Americans are an admixed population, resulting from intermating between individuals of African and European descent. A panel of ancestry informative markers (AIMs), which are markers whose alleles are differentially distributed in the ancestral populations, is needed to conduct MALD analyses and panels were developed for African Americans [11] and Hispanic Americans [12]. This approach is a cost-efficient compromise between whole genome linkage analyses and more expensive GWAS [13]. MALD identified the non-muscle myosin heavy chain 9 (*MYH9*) gene underlying susceptibility to non-diabetic and diabetic ESRD in African Americans. The following sections review gene associations in diabetes-associated nephropathy (DN), non diabetes-associated nephropathies and genes modulating renal function in general populations.

2. Diabetes-associated nephropathy (DN)

Diabetes mellitus is a heterogeneous disorder with variable degrees of insulin resistance and deficiency contributing to hyperglycemia. Several genes have been implicated in DN. SNPs in a non-coding region of chromosome 3q22 are strongly associated with type 1 DN in Europeans [14] and a discordant sib pair analysis confirmed prior associations between type 1 DN and regions on 1q, 20p and 3q [15*]. Associations between DN and promoter polymorphisms in the erythropoietin gene (*EPO*) [16*] and variants in the superoxide dismutase 1 (*SOD1*) have been identified [17].

A GWAS was performed in Genetics of Kidneys in Diabetes (GoKinD) participants and replicated in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications. These European Americans cohorts with type 1 diabetes revealed association with loci near the 4.1 protein ezrin, radixin, moesin (FERM) domain containing 3 (*FRMD3*) gene and the cysteinyl-tRNA synthetase (*CARS*) gene [18*]. Association p-values barely missed genome-wide significance. We focus on 4 replicated DN susceptibility genes, below.

2.1 Plasmacytoma variant translocation (PVT1) gene—*PVT1* was found to be associated with type 2 DN in Pima Indians using a pooled GWAS in small numbers of cases and controls [19]. Replication in Europeans with type 1 diabetes-associated ESRD was detected in GoKinD [20]. The associated *PVT1* SNP rs13447075 is located within the coding region of a transcript variant and this isoform was expressed in human mesangial, cortical epithelial, epithelial, and proximal tubule cells, suggesting a role in pathogenesis.

2.2 Engulfment and Cell Motility 1 (ELMO1) gene—*ELMO1*, involved in phagocytosis of dying cells, is required for cell migration and alteration in cell shape [21]. Several variants in this large gene are associated with type 2 DN. Disease association was originally detected in a Japanese sample using GWAS [22], replicated in African Americans [23] and further replicated in European Americans with type 1 DN [24]. As for *PVT1*, nephropathy in type 1 and type 2 diabetes clusters in single families and may share common predisposition. *ELMO1* expression is increased in an animal model of chronic glomerulonephritis, resulting in over expression of extracellular matrix proteins and loss of cell adhesive properties [25]. Polymorphisms in different regions of *ELMO1* are associated with DN in select ethnic groups: intron 18 in Japanese, intron 13 in African Americans, and predominantly intron 16 in European Americans; however, different polymorphisms appear to produce a common DN phenotype.

2.3 Carnosinase 1 and Carnosinase 2 (CNDP1 and CNDP2) genes—The protein encoded by *CNDP1* on chromosome 18q is expressed in the brain and kidney. Consistent evidence of linkage to 18q strongly supported the existence of a DN gene in this region. [26-28]. Involvement of *CNDP1* in DN was detected by the Mannheim group [29]. Association has since been replicated in European Americans with type 2 DN [30], but not in type 1 DN [31]. The 5 leucine-5 leucine (5L-5L) gene variant is protective against DN in an autosomal recessive fashion. Cos-7 cells transfected with the 5L variant secreted less carnosinase than did cells expressing 6L or 7L, demonstrating that this hydrophobic leucine stretch was of importance for targeting the protein into the secretory pathway [32]. Carnosine is a scavenger of oxygen free radicals, inhibits formation of advanced glycosylation end-products and inhibits TGFβ production. Individuals who are *CNDP1* 5L-5L homozygotes secrete less carnosinase and are expected to have higher carnosine levels with protection from DN. Protection from DN afforded by 5L-5L homozygosity in *CNDP1* appears to be masked by the effects of additional *CNDP1* and *CNDP2* haplotypes in African Americans [33].

2.4 Endothelial nitric oxide synthase (eNOS) gene—Proteinuria and glomerulosclerosis result in animals treated with chronic nitric oxide blockade [34]. The T-786C polymorphism in *eNOS* reduces gene promoter activity and is associated with coronary disease [35]. *eNOS3* associations have widely been observed in progressive DN [36-40]].

3. Non-diabetic nephropathy

FSGS is a common pattern of kidney injury disproportionately affecting African Americans and often leading to ESRD. Several gene variants were known to be associated with FSGS; however, they failed to account for the majority of adult cases until detection of the non-muscle

myosin heavy chain 9 gene (*MYH9*). In addition, microRNAs appear to be involved in the development of glomerulosclerosis [41] and DN [42].

3.1 Non-muscle heavy chain 9 (MYH9) gene—*MYH9* is a podocyte-expressed gene encoding nonmuscle myosin IIA. This gene contributes to approximately 43% of ESRD in African Americans, playing major roles in idiopathic FSGS, human immunodeficiency virus-associated nephropathy (HIVAN), and global glomerulosclerosis (historically labeled "hypertensive ESRD"). Kopp et al. [43**] and Kao et al. [44**] identified *MYH9* variants associated with ESRD in independent African American samples. Kopp reported the *MYH9* E1 haplotype conferred an odds ratio of 4.7 for idiopathic FSGS and 5.9 for HIVAN. The E1 haplotype is present in 60% of African-Americans, compared to 4% of European-Americans. Kao et al. estimated that the prevalence of ESRD would be reduced by 70% if African Americans had inherited European ancestry at the *MYH9* locus. We [45] demonstrated that *MYH9* variants were weakly associated with albuminuria in hypertensive African-American, but strongly associated with ESRD previously thought due to hypertension [46**;47]. Global glomerulosclerosis in African Americans, historically labeled "hypertensive nephrosclerosis", is predominantly *MYH9*-associated and in the spectrum of FSGS [48]. Linkage was detected on chromosome 22q13 in Europeans with CKD, in the genomic region of *MYH9* [49]. *MYH9* also contributed to 16% of clinically diagnosed type 2 DN in African Americans [50]. *MYH9* polymorphisms underlie most of the excess risk for non-diabetic ESRD in African Americans relative to European Americans and will force re-classification of the spectrum of FSGS/global glomerulosclerosis. Possible mechanisms whereby *MYH9* may induce CKD include podocyte cytoskeletal abnormalities resulting from improper actin movement or platelet dysfunction as seen in May Hegglin anomaly [51]. Chromogranin A (*CHGA*) gene polymorphisms also contribute to hypertension-associated ESRD in African Americans [52*]. The effects of *CHGA* may be mediated via endothelin and TGFβ1, released by endothelial and mesangial cells [53*].

3.2 Nephrosis homolog (NPHS) gene family—Three genes in the *NPHS* family are associated with CKD. Mitochondrial DNA tRNA leucine nephrin-(*NPHS1*) endoding nephrin, a transmembrane adhesion molecule localizing to signaling domains within the slit diaphragm of the podocyte, modulate urinary protein excretion. Mutations are associated with congenital nephrotic syndrome of the Finnish type [54]. Other variants are associated with glomerulosclerosis and steroid-resistant nephrotic syndrome (SRNS) in children of European [55;56] and Japanese descent [57].

NPHS2 on chromosome 1q25-q31 encodes the glomerular protein podocin, involved in regulation of glomerular permeability [58]. Mutations in *NPHS2* are frequently observed in childhood SRNS and a variant are implicated in recurrence of proteinuria after kidney transplantation [59]. Phospholipase C epsilon 1 (*PLCE1*), also labeled *NPHS3*, is associated with diffuse mesangial sclerosis, an idiopathic childhood renal disease that frequently progresses to ESRD [60]. Other genes causing Mendelian forms of FSGS include alpha-actinin 4 (*ACTN4*), transient receptor potential cation channel 6 (*TRPC6*), CD2-associated protein-(*CD2AP*), and Wilm's Tumor-1 (*WT1*) [61-64]. *ACTN4* polymorphisms confer a distinctive phenotype [65*].

3.3 HIV-associated nephropathy—Without antiretroviral therapy, HIVAN can be an aggressive kidney disease in African Americans. HIVAN is a variant of FSGS characterized by the collapse of the glomerular tuft with podocyte hypertrophy and hyperplasia [66]. In addition to *MYH9*, genes involved include *CCR5* (promoter region and delta 32 deletion), the angiotensin II type 1 receptor (*AT1R*), *CCR2-V64I*, *SDF-1*, a copy number polymorphism *CCL3L1*, *RANTES* and various HLA types [67;68]. Variants in the chemokine (C-C motif) receptor 5, a receptor for pro-inflammatory chemokines, have been associated kidney disease

and kidney transplant acute rejection [69], while others have shown protection from inflammation-associated mortality in dialysis patients [70].

It is likely that second hits, gene-gene and/or gene-environment interactions, are necessary to induce HIVAN. Papeta et al. [71**] demonstrated that transcript levels of *NPHS2* and other podocyte-expressed genes function in integrated fashions and gene polymorphisms induced by susceptibility to HIVAN appear to perturb regulatory pathways inducing collapsing FSGS.

4. Genes regulating renal function in the general population

UMOD encodes uromodulin or Tamm-Horsfall protein, the most abundant protein in normal urine. Involvement of this gene in kidney function was suggested by a linkage peak on chromosome 16p [72;73]. *UMOD* mutations are associated with the spectrum of medullary cystic kidney disease type 2, familial juvenile hyperuricemic nephropathy, and glomerulocystic kidney disease [74. Benetti [75] identified a *UMOD* variant (NM_003361.2:c.149G→C; p.Cys50Ser) associated with absence of urinary uromodulin excretion and Köttgen et al. [76**] found that SNP rs12917707 near *UMOD* demonstrated strong association with CKD (p-value 5×10^{-16}) in a GWAS, as well as implicated *SHROOM3* (involved in epithelial cell shape regulation), *JAG1* and *STC1* as associated with CKD. These studies were conducted in individuals of European descent. *TCF7L2* gene polymorphism, strongly associated with susceptibility to type 2 diabetes mellitus, may also play a role in the progression of non-diabetic nephropathies [77]. In Japanese populations, *UMOD* variants were associated with hypertension [78] and *MMP1* and *UCP2* were associated with CKD [79] (see Table).

5. Role of refined phenotypes in CKD gene mapping

A key component in the success of any genetic study is appropriate definition of phenotypes. Phenotypic data should be subjected to the same levels of quality control as genotypic data, since poorly defined phenotypes lead to loss of power and inability to replicate findings. Biomarkers or endophenotypes, defined as clinical entities closer to the underlying biology than mere disease-associated symptoms, can be valuables tools in gene mapping. Variation in gene expression offers valuable insight into mechanisms underlying susceptibility to complex disease. Recently, traditional gene mapping strategies including linkage and association have been applied to gene expression data by treating them as outcome (quantitative or expression quantitative trait loci; eQTL) variables [80]. eQTLs are heritable [81] and can lead to significant gain in power when used in association analysis with SNPs [82]. The potential for these refined phenotypes to map CKD genes has been demonstrated. Ju et al. [83*] showed that protein expression, a subcomponent of gene expression, predicts progressive renal fibrosis in mice and may be useful molecular predictors of human CKD progression. Murphy et al. [84] applied differential gene expression technologies to describe the role of proteins such as CTGF, which acts as a mediator of TGF-β1-driven matrix production within the diabetic kidney and Gremlin, whose expression level in kidney biopsies in DN patients is higher than that observed in normal kidney.

6. Future directions

Despite initial enthusiasm for MALD and current interest in GWAS, the variants that these methods identified only account for a small fraction of the heritability of most common traits. This suggests that consideration must be given to other sources of variation including gene-gene [85] and gene-environment interactions [86], as well as copy number variation (CNV) [87], in addition to improving statistical methods addressing lack of power, phenotypic and population heterogeneity and multiple testing. There is also a need to develop more efficient ways to combine data from sources such as gene expression and GWAS data. These efforts are underway, as reviewed by Nica and Dermitzakis [88].

7. Conclusions

It has now been proven that susceptibility to DN and non-diabetic nephropathy is partly mediated by genetic predisposition. *MYH9* is an important nephropathy susceptibility gene underlying 43% of diverse forms of severe kidney disease in African Americans. Approximately 4% (for idiopathic FSGS) to 20% (for HIVAN) of African Americans inheriting two *MYH9* risk variants may develop nephropathy. Additional genes reveal strong and reliable association with diabetic nephropathy. Screening tests and novel therapies derived from these genetic associations may offer new hope for slowing the worldwide epidemic of kidney disease.

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Table 1

Genes associated with diabetic nephropathy, non-diabetic nephropathy and regulation of renal function (with relevant references)

Diabetic Nephropathy	Non-diabetic nephropathies	Regulation of renal function
EPO [16]	*MYH9* [43-50]	*UMOD* [74-76]
SOD1 [17]	*NPHS1* [54,57]	*SHROOM3*, *JAG1* and *STC1*[76]
CARS [18]	*CHGA* [52-53]	*TCF7L2* [77]
PVT1 [19-20]	*NPHS2* [58-59]	*MMP1* and *UCP2* [79]
ELMO1 [22-24]	*PLCE1* [60]	
CNDP1, *CNDP2* [29-33]	*ACTN4* [61,65]	
eNOS [36-40]	*TRPC6* [63]	