Hypertension

REVIEW

Emerging Insights Into Chronic Renal Disease Pathogenesis in Hypertension From Human and Animal Genomic Studies

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ABSTRACT: The pathogenic links between elevated blood pressure and chronic kidney disease remain obscure. This article examines progress in population genetics and in animal models of hypertension and chronic kidney disease. It also provides a critique of the application of genome-wide association studies to understanding the heritability of renal function. Emerging themes identified indicate that heritable risk of chronic kidney disease in hypertension can arise from genetic variation in (1) glomerular and tubular protein handling mechanisms; (2) autoregulatory capacity of the renal vasculature; and (3) innate and adaptive immune mechanisms. Increased prevalence of hypertension-associated chronic kidney disease that occurs with aging may reflect amplification of heritable risks by normal aging processes affecting immunity and autoregulation.

Key Words: blood pressure ■ genome-wide association study ■ genomic structural variation ■ kidney diseases ■ prevalence

The prevalence of chronic kidney disease (CKD; stages 1–4) in US adults is 15% and increases with age, rising to 38% in people 65 and older.[1] Prevalence is greater in the non-Hispanic Black population (16%) than other ethnic groups (Hispanic [14%], non-Hispanic White [13%], and non-Hispanic Asian [12%] populations). In population-scale genomic studies, the diagnosis of CKD relies on indirect assessments including excretion of protein and serum levels of markers, such as creatinine and cystatin. Renal biopsy data is helpful from a diagnostic and prognostic standpoint but is not required for CKD staging, and there is insufficient collated biopsy information available to directly inform large-scale population studies.[2] Although high blood pressure (BP) increases CKD risk, other factors also influence risk as CKD prevalence ranges from 1 in 3.6 to 4.5 in diagnosed and undiagnosed hypertensives.[3]

The pathogenic mechanisms connecting hypertension to CKD are not well understood. Heritable risk has created hope that population genetic studies associating phenotypes of renal function with underlying genetic variation will point to disease mechanisms indicated by the function of genes associated with disease. Studies of genetic risk in rat models of heritable hypertensive renal diseases have also been pursued in the expectation that these studies provide an alternative path to uncover genes involved. These studies have progressed sufficiently to illustrate several themes and to examine obstacles to further progress.

HERITABILITY OF RISK OF RENAL DISEASE

Population genetics studies require evidence of heritability. The most recent population-based family studies indicate that risk of CKD is increased 3 fold in individuals with a first-degree relative affected by CKD.[4] Heritability of renal function, the proportion of trait variation attributable to genetic variation, calculated from twin-pair correlations of estimated glomerular filtration rate (eGFR) and albuminuria[5] is 77.6% and 45.2%, respectively. Heritability of GFR measured as creatinine clearance is 33% to 53%.[6] Albuminuria and eGFR are used in population-based genome-wide association studies (GWAS) because they are practical to assess in large scale. They present some limitations: urinary albumin creatinine ratio

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REVIEW

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
FHH	Fawn-Hooded Hypertensive
GWAS	genome-wide association studies
NF-κB	nuclear factor-κB
PKC	protein kinase C
SNP	single-nucleotide polymorphisms
SV	structural variation
TNF	tumor necrosis factor
UMOD	Uromodulin

requires the independent measurement of 2 variables, each introducing error; eGFR typically uses serum creatinine and requires adjustments depending on patient variables.[7] Serum creatinine is influenced by heritable effects on creatinine metabolism, in addition to difference in GFR, leading to the recent introduction of blood urea nitrogen in GWAS studies.[8]

GWAS studies test for association of renal function with allelic state at each of a very large number of genome-wide single-nucleotide polymorphisms (SNPs). The resulting multiple hypothesis testing is generally addressed in 2 ways: by elevation of the threshold for statistical significance for any single SNP/phenotype association, and; by retesting associations observed in a discovery population in a replication population. This approach requires very large subject numbers and multiple, often multi-national, populations are used to achieve these numbers. This transancestry population sample pooling may obscure genetic variation that is subpopulation specific. Another obstacle in GWAS arises from its reliance on a single class of genetic variation. New long-read sequencing technologies reveal an important role for genomic structural variation (SV) in trait divergence within populations.[9,10] SV's range upwards from 50 base pairs and include larger events, such as duplication, insertion, deletion, transposition, and inversion. Population SV is still being described, so it remains unclear to what extent SVs can be imputed from adjacent SNP genotypes.[11–13] Furthermore, some SVs can confound SNP genotyping (Figure 1), obstructing discovery of SNP association in regions containing SV.

PROGRESS IN GWAS

An important rationale for large-scale population genetics studies was the view that genetic variants creating common polygenic disease susceptibility might be frequent in a population and shared across populations of different ancestry. This common disease:common variant hypothesis posited that the set of trait-associated variants is concise (ie, not composed of a very large number of unique variants) and allows a tractable discovery task.[14,15] In general, this has not been the outcome. Most GWAS studies of disease susceptibility have accounted for only a portion of observed heritability. This missing heritability has been the source of much conjecture. In general, GWAS does find and confirm SNP associations, but understanding of pathogenesis has generally not emerged.

The most recent GWAS of renal function studied in excess of 750 000 subjects, with a replication population of ≈280 000 subjects.[8] Heritability in this study population of renal function was estimated at 39%. A total of 308 index SNPs were found that explained 19.6% of eGFR heritability. Thus, 308 SNP's account for ≈8% of the total (heritable and nonheritable) eGFR variation, on average 0.025% per SNP. These small effects leave 80% of the heritability missing. In the replication cohort, 264 of these SNPs were significant: even with small effect sizes, SNP associations are largely confirmed. Among replicated eGFR SNP associations, 34 SNPs were significantly associated with blood urea nitrogen. The replicated SNPs were then studied for association with CKD in the CKDGen studies (≈625 000 subjects including ≈64 000 CKD cases). This analysis found that 23 of 264 SNPs significantly associate with CKD. These studies epitomize the dichotomy of complex disease association studies: replicable SNP associations are evident but provide little insight into disease processes. There appear to be other effects that are heritable that cannot be mapped in these studies.

Several explanations for the inability of GWAS to account fully for the heritability of CKD risk have been considered. For example, heritability arises from a very large number of small effect variants, and all are discoverable with population sizes not yet achieved. This has been termed the omnigenic thesis of heritability.[16] Another possible explanation is that the genetic architecture of renal function is attributed to rare variants that have large effects but that are highly heterogenous. These may go undiscovered in GWAS because they are sufficiently rare that the SNP genotypes linked to these variants are most often linked to wild-type sequences that are not disease associated. The reliance of GWAS on genotyping arrays that address very large numbers of SNPs provides a one-dimensional view of genetic association. SNPs reflect variants largely obtained from the analysis of human genome sequencing data and provide information that is genotyped accurately and inexpensively. This sequencing used principally short-read methods that are not instructive about SV longer than the short reads.

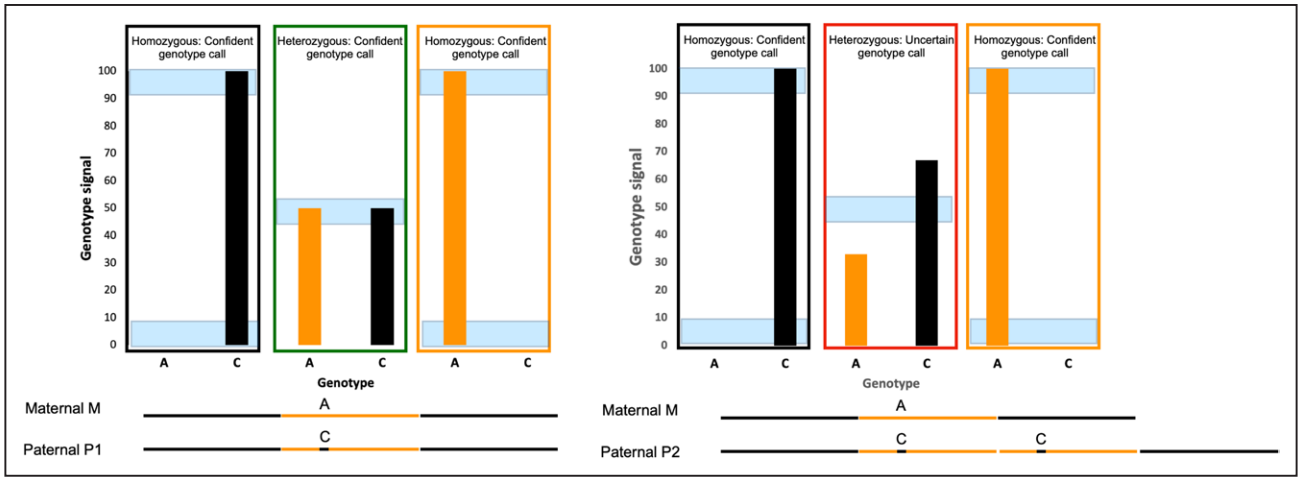

Figure 1. The presence of structural variation (SV) can confound single-nucleotide polymorphism (SNP) genotyping. **Left**, At locus X an individual has inherited from their father a chromosomal segment (orange line) containing an SNP, while the corresponding chromosomal segment inherited from the mother lacks this SNP (C vs A). A high-throughput genotyping assay is developed that is able to call this SNP by accurately discriminating the genotyping signals that occur when an individual is homozygous for the paternal genotype (homozygous C), heterozygous, or homozygous for the maternal genotype (homozygous A). To do so, the assay must generate signals reflecting genotype that are sufficiently restricted (blue shading) to values near 0%, 50%, and 100% which are the expected values for each of the 3 Mendelian states. **Right**, The orange chromosomal region has been the subject of a duplication event at some point in evolution resulting in individuals that may have one or 2 copies of this segment. This duplication event occurred on a chromosome bearing the C variant. This individual has inherited an unduplicated orange segment from the maternal lineage and has obtained a duplicated paternal segment in which 2 copies of the SNP variant are present. The genotyping assay produces unexpected values for this variant because the number of copies of the C variant is double and the resulting signals are twice as strong as those arising from the A allele. As a consequence the genotyping assay for this individual (red box) produces values that fall outside of the expected distribution. Because of unexpected performance (since the duplication event is not known) the assay is eliminated from further consideration for inclusion in a high-throughput multiplex assay system. Potentially important biological variation is present. In the population there may exist all 3 alleles described here: M, P1 and P2. Not only is this genetic variation not captured by the assay because it does not fulfill expected signal ratios, but it is excluded from informing genotype-phenotype associations that may arise from structural variation.

GWAS SNP ARRAYS FAIL TO ADEQUATELY ASSESS GENETIC VARIATION IN IMMUNE RECEPTORS

Elevated renal perfusion pressure results in the migration of adaptive immune cells into the kidney. The existence of this phenomenon occurring in response to elevated BP, and independent of immune signaling induced by hypertensive agents used to elevate BP, has been elegantly shown by Shimada et al.[17] Acute renal injury and associated tissue damage initiate sterile immune responses arising from danger signals conveyed by damage-associated molecular patterns.[18] Since the chronic renal disease is associated with acute injury[19] and may, in the presence of hypertension, reflect the persistent effect of injury mechanisms, the sustained activation of immune responses may play a role in CKD in hypertensives. The involvement of immune cells, notably T and B lymphocytes, in hypertension and renal injury has been extensively examined in animal models.[20–23] These lymphocytes are typified by the cell surface expression of T- and B-cell receptors that are a key characteristic of these cells that drives the immunologic process by which they may contribute to renal injury. These adaptive immune receptors are highly divergent in the population and much of this divergence arises from SV. Thus, while key receptors on immune cells are central to renal injury, the natural genetic variation in these hypervariable receptors cannot be adequately addressed by SNP arrays, and consequently, they are dramatically underrepresented on these arrays. The extent of this underrepresentation has recently been surveyed by Mikocziova et al.[24] Recent efforts to generate accurate and complete assemblies of immunoglobulin, T-cell receptor, and natural killer cell receptors in a single individual have exploited state of the art long-read and other mapping and assembly approaches.[25] They have concluded that a full accurate and complete assembly of variation in some of these regions in a single individual is a technical challenge that has not yet been overcome and will require further methodological improvements. These problematic regions of the genome, and others of perhaps similar complexity and biological importance, underscore that the notion that SNP-based GWAS is a comprehensive tool for uncovering genetic variation contributing to disease traits is one in need of re-assessment.

SV AND COMPLEX DISEASE INHERITANCE

Disease association studies may advance when population mapping approaches are able to consider SV

variation. SV has been predicted to have a high phenotypic impact[26] and recent studies have begun to assess this proposition directly.[10] Newer high accuracy long-read sequencing[27] supported by optical mapping techniques[28] have begun to provide a rich source of information about genomic SV.[9,29–32] The features of SV in humans have been summarized recently by Eichler[33] who points out that emerging data sets applying long-read sequencing and assembly to human genomes have begun to re-shape our view of allocation of genetic variation in the genome between the SNPs and larger-scale variation and indicates that bases with SNP variation represent only 7.6% of the total variant bases in the human genome. The SNP variation assessed in GWAS represents a small portion of the total genetic variation and may account for a similar portion of the phenotypic variation among humans. Recently completed telomere to telomere sequencing of the human genome has revealed the 8% of the genome that was previously not represented in the data sets used to devise GWAS SNP arrays and much of this missing genome was the result of complex SV.[34,35] Population-scale studies to assemble a deep collection of SV have begun,[9,36–38] however, the technical approaches that allowed SNP-based association studies to sample comprehensive collections of SNPs in large populations has not yet emerged for SV.

GWAS SUCCESS AND PROSPECTS

Apolipoprotein 1

Discovery of Black patient-specific CKD risk alleles has been made in using a modified GWAS approach called admixture mapping.[39,40] This exploits recent admixture in American persons of African ancestry with other populations and postulates that SNP marker variation enriched in the admixed population includes genomic regions associated with CKD and this might be mapped by combining ancestral divergence in the genome with disease susceptibility mapping. A locus reflecting African ancestry was identified on chromosome 22 that was associated with focal segmental glomerulosclerosis and hypertensive renal disease.[40] In subjects homozygous for risk alleles, focal segmental glomerulosclerosis risk was increased by 5-fold and hypertensive renal disease risk was increased 2.2-fold. Variation in the *APOL1* gene drives the renal disease effect.[41]

APOL1 encodes an apolipoprotein providing innate immune defense against trypanosome infection.[42] Such infection is endemic in West Africa. In this locale, the human immune system and parasitic trypanosomes have engaged in a genetic arms race in which mutations in trypanosome defense mechanisms have been met by the emergence of *APOL1* mutations that overcome adapted pathogen resistance.[43] Resistance to African trypanosomal diseases such as sleeping sickness likely provide a fitness benefit that has caused such variant *APOL1* alleles to rise in frequency in endemic regions.[42] There are 2 variant alleles of *APOL1* that confer CKD susceptibility, both lead to amino acid changes in APOL1 (Figure 2). Inheritance of a single variant allele creates only a slight increased risk of nephropathy, while the presence of 2 risk alleles leads to a marked increase in risk.[44] In addition to amplifying renal disease risk in hypertension, pathogenic *APOL1*-mediated disease may be increased in states of innate immunity activation. Consequently, *APOL1* may influence risk of CKD development in HIV[44] and coronavirus disease 2019 (COVID-19)[45–47] infection and may occur in genetically susceptible patients treated with interferons.[48]

The disease-associated alleles have been recreated experimentally in both cellular and animal models (zebrafish and mouse).[49–51] The mechanism of pathogenesis remains obscure. APOL1 may participate in functional specialization of the podocyte. The minor effects of presence of a single risk allele implies a loss of function mutation, but this explanation is not fully satisfactory. The different amino acid changes in the 2 risk alleles both affect a similar region of the protein, so each allele seems likely to contribute to loss of function. However, amplification of disease in the presence of strong upregulation of expression of the *APOL1* gene in an interferon-dependent manner suggests that disease results from gain of function-mediated injury.[48,52,53] It also suggests that disease risk arises from the combined effects of genetic variation with additional triggers, including hypertension. Thus, risk alleles are necessary but not sufficient for disease.[54] It has been observed that overexpression of even the nonrisk *APOL1* allele in the podocyte can produce injury,[55] suggesting disruption of cellular functions, possibly including those involving proteins that interact with APOL1.

Most recently, a mechanism of APOL1 pathogenesis has been proposed involving interactions with APOL3 and phosphatidylinositol 4-kinase, a Golgi membrane-localized enzyme involved in vesicular trafficking and mitochondrial fusion.[56] In podocytes APOL1 resides at the Golgi in contact with APOL3. Deletion of *APOL3* increases mitochondrial fission, an event recapitulated in trypanosomes that have ingested host APOL1.[57] Reduced levels of PI(4)P are observed in podocytes expressing *APOL1* variants and in biopsies from patients with disease risk alleles of *APOL1*.[57] Variants of *APOL1* have been proposed to inactivate APOL3 function, leading to reduced phosphatidylinositol 4-kinase activity, with a consequent alteration in vesicular trafficking activity in podocytes, possibly connected to alterations in the podocyte actomyosin cytoskeleton.[56] *APOL3* null alleles also increase risk of nondiabetic nephropathy.[58] At this time, the mechanism by which risk alleles of *APOL1* create renal injury remains an active area of investigation.

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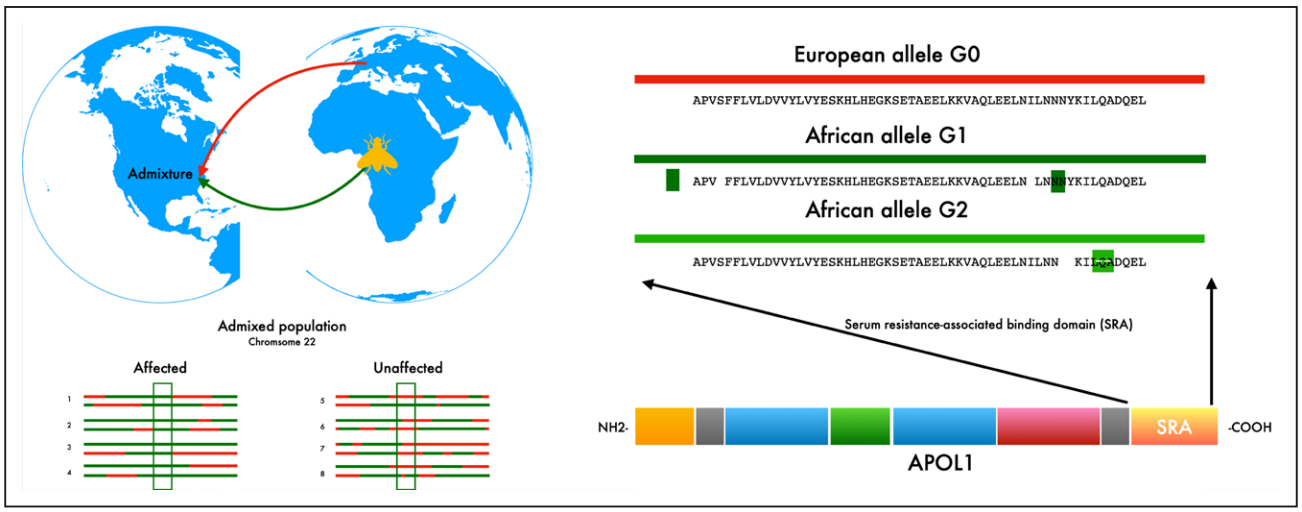

Figure 2. Discovery of important role of *APOL1* genetic variation in renal injury susceptibility in US persons with African ancestry. **Left**, Recent admixture between Americans with European and African ancestry allows the following question to be examined: Can regions of the genome in Black individuals that experience renal disease be identified that in the affected part of the Black population predominantly comprise ancestral alleles of African origin? This admixture mapping approach identified a region of chromosome 22 in which there is a high incidence of homozygosity of ancestral African alleles in persons affected with nondiabetic renal disease (predominantly hypertensive disease). In this locus lies the *APOL1* gene that contributes to innate immunity to infection with insect-borne trypanosome parasites resulting in sleeping sickness. Such infection is endemic in Central West Africa but not in Europe. **Right**, APOL1 infection resistance results from the action of a serum-resistance associated binding domain. Evolution of trypanosome parasite resistance to APOL1 has resulted in an arms race in which genetic variants in *APOL1* that overcome this resistance are favored and increase in prevalence in endemic regions. Two such *APOL1* variants have been identified that are present in some individuals with African ancestry and that restore the anti-trypanosomal effects of APOL1. When an individual inherits either of these variants (G1 and G2) in homozygosity or inherits one of each of G1 and G2 (compound heterozygosity) risk of renal disease is increased. This risk may be amplified by increased gene expression of *APOL1*. As a gene of innate immunity its expression has been shown to be controlled by host immune signaling. This may include signals resulting from inflammation occurring when the kidney experiences elevated blood pressure. Other inflammatory conditions such as HIV and coronavirus disease 2019 (COVID-19) infection and sickle cell disease may also amplify risk or renal disease arising from these genetic variants.

It is important to retain a suitable perspective on the population risk attributable to *APOL1* variation in the Black population. Only 13% of Black individuals possess the risk genotype of *APOL1*. Among Black participants in the Dallas Heart Study 69.8% of individuals with nondiabetic CKD lacked the *APOL1* risk genotype and 50% of Black patients with end-stage renal disease had the risk genotype.[59] Among the 50% with end-stage disease who lacked the risk genotype, it is likely that other genetic factors contribute to risk of CKD, and these unknown risk variants may be shared with populations lacking recent African ancestry.

Uromodulin

UMOD (Uromodulin) encodes the most abundant urinary protein, also known as Tamm-Horsfall protein, which is produced in epithelial cells of the medullary thick ascending limb and distal convoluted tubule and secreted into urine and blood. Rare variants in uromodulin have previously been associated with renal disease, notably autosomal dominant tubulointerstitial nephropathy.[60] However, GWAS association between *UMOD* variation and loss of renal function has been attributed to a common variation representing the highly prevalent ancestral allele that modifies *UMOD* gene expression.[61,62] The genetic and pathogenic insights into *UMOD* function and variation have been recently thoroughly reviewed.[63,64] Renal functions of UMOD are complex and include a potential role as an antibacterial agent providing defense from retrograde bacterial colonization of the urinary tract to interactions with tubular mechanisms regulating sodium reabsorption. No clear mechanism of pathogenesis has yet emerged to connect genetic variation in the *UMOD* locus with loss of renal function.

EXPRESSION VARIANTS

Several groups have investigated whether GWAS associations arising outside of genes may induce effects by altering nearby gene expression. Xu et al[65] showed that 3 genes, *NAT8B*, *CASP9*, and *MUC1* initially identified in GWAS have expression traits linked to eGFR. Increased expression of a common *MUC1* splice variant was a plausible explanation for its renal function GWAS signal. Ko et al[66] report an alternative approach in which RNA-seq analysis of gene expression in 96 kidney cortex samples was performed. Expression of nearly 2000 out of 17 000 genes examined was associated with nearby SNP, yielding cis-expression quantitative trait loci, or cis-eQTLs. Kidney gene expression SNPs were enriched with SNPs identified in GWAS mapping. Additional filtering produced a list of genes, including *PGAP3*, *SPATA5L1*, *ALMSIP1*, *PIGU, EEF1AKMT2*, and *MANBA*, likely able to influence renal function through heritable effects on

their expression. Additional analysis of *MANBA* showed its risk allele was associated with a 50% reduction in its expression in normal human kidney.[66] Rare heterozygous loss of function mutation of *MANBA* is associated with loss of renal function in humans.[67] Nephrotoxic renal injury is greater in mice with monoallelic or biallelic loss of *MANBA* function and toxic acute tubule injury induced inflammasome activation and fibrosis in the latter.[67] *MANBA* may contribute to population renal disease risk by modifying adaptation to renal toxicant exposure.

In the genome, *MANBA* is colocalized with *NFKB1*, a gene also implicated by GWAS in CKD. Both *NFKB1/MANBA* contain promoter sequence variation affecting regulation of their expression,[68] and this region is associated with many autoimmune diseases, including Crohn disease, ulcerative colitis, and primary biliary cholangitis.[68–72] Like CKD, these diseases also involve inflammation and immune cell infiltration for which *NFKB1* is a key inflammatory signaling gene. Two other genes within the nuclear factor kappaB (NF-κB) signaling pathway, *NFATC1* and *PTPRO*, have emerged in renal GWAS studies.[73] Protein tyrosine phosphatase, receptor O (PTPRO) and NF-κB are activated by T- and B-cell signaling,[74,75] while NFATC1 is the major transcription factor responding to such signals.[76] Variants generating gene expression effects may act through more than one gene in the *NFKB1/MANBA* locus to drive disease risk.

ANIMAL MODEL APPROACHES TO GENETICS OF PROGRESSIVE RENAL DISEASE

Inbred rodent models of CKD harbor natural genetic variation contributing to disease pathogenesis. Full inbreeding reduces genetic complexity because each pair of maternal and paternal autosomes are identical. These models also allow confirmation of mapping results by targeted backcrossing of chromosomal segments between unaffected and affected inbred lines (congenic line creation). Once disease loci have been proven, genetic variation associated with specific genes in the congenic segment can be investigated by approaches including whole genome sequencing, targeted gene deletion or amplification, and analysis of gene expression, alternative gene splicing and protein abundance. While human population genetics studies produce statistical findings, animal models allow investigation of kidney tissue during disease progression and of the biological consequences of disease gene variation.

Munich Wistar Fromter Rat

The capacities of such approaches are exemplified in the Munich Wistar Fromter rat, a model of BP-associated progressive renal disease.[77] Mapping studies indicated that locus on chromosome 6 was linked to renal injury.[78] A congenic line in which the chromosome 6 genomic region from the hypertensive but albuminuria resistant spontaneously hypertensive rat (SHR/Rkb) line was substituted into Munich Wistar Fromter narrowed the causative variation to a gene-rich 4.9 Mb region containing 75 protein-coding genes.[77] To identify the causal variation, genomic resequencing was performed allowing variant comparison between the lines. Five genes in the region were affected by potentially deleterious mutation, however, none appeared to be an explicit candidate gene for renal injury. Expression of genes in this region in isolated glomeruli from SHR and Munich Wistar Fromter revealed increased gene expression of *Tmem63c* in Munich Wistar Fromter compared with SHR and the congenic line, indicating likely cis-regulation of expression. Immunohistochemistry indicated podocyte restriction of *Tmem63c* expression. *Tmem63c* functional studies were performed in zebrafish and reduced gene function correlated with increased urinary protein filtration which was partially rescued by expression of *Tmem63c*.[77] These studies exemplify approaches available in animal models to identify, confirm and further investigate natural genetic variation that may drive pressure-related loss of renal function.

Fawn-Hooded Hypertensive Rat

Roman et al have discovered genetic variation that contributes to BP-driven renal injury in the Fawn-Hooded Hypertensive (FHH) rat. FHH experiences focal segmental glomerulosclerosis and proteinuria with increasing BP as animals age.[79,80] Their work uncovered 3 distinct pathogenic mechanisms of renal disease. Genetic variation in *Shroom3* in FHH alters its interactions with actin and contributes to podocyte foot process fusion and albuminuria.[81] *Shroom3* has also been mapped in human populations as containing variation that can influence renal function and *Shroom3* antagonism affects podocyte structure in mice.[82] Albuminuria in FHH arises from variation in *Rab38* that acts to reduce tubular reuptake of filtered protein.[83] *Rab38* has been associated with diabetes-associated proteinuria in human populations.[84] Single-nucleotide variation in gamma adducin (*Add3*), a cytoskeletal protein, also contributes to renal injury in FHH. The *Add3* variant present in FHH impairs physiological autoregulation of renal blood flow. Autoregulation occurs by intrinsic myogenic reflex contraction of renal blood vessels with increasing perfusion pressure which limits increases in blood flow and reduces transmission of elevated pressure to the glomerulus. The role of *Add3* variation was uncovered by mapping of a chromosome 1 locus contributing to disease. Creation of congenic animals narrowed this region to ≈2 Mb. Genetic variation isolated in this ≈2 Mb segment affects the renovascular myogenic reflex.[85] This autoregulatory reflex requires transmembrane ion

fluxes which were investigated to reveal an effect of *Add3* variation to increase BK channel-opening probability. This may act to limit calcium influx into vascular smooth muscle cells resulting from pressure-induced depolarization,[86] and thereby impair development of pressure-driven myogenic tone. Interestingly, Hunt et al[6] mapped a human GFR locus to the region of the human genome containing *Add3*. Thus, in FHH 3 distinct mechanisms of renal injury have been identified.

SHR

Another well-established rat model of CKD is the spontaneously hypertensive rat, SHR. This strain was produced by selective breeding on the trait of elevated BP, generating animals with elevated systolic BP (180–200 mm Hg).[87] Inbreeding to fix the hypertensive genetic variation was performed in 3 parallel lineages. Among the A, but not the B and C, lineages it was observed that hypertension resulted in stroke and that stroke was preceded by the emergence of progressive proteinuric renal disease.[88] Fixation of stroke-risk alleles resulted in SHR-A3, commonly called the stroke-prone SHR, SHRSP.[88] Renal autoregulatory capacity is identical in SHR lines that differ in susceptibility to renal injury.[89,90] Renal injury emerges when systolic BP exceeds the autoregulatory range (≈18 weeks of age)[91] and is accelerated by salt loading.[92] Before emergence of renal injury, SHR-A3 has slightly higher BP than other SHR lines. Genetic mapping in a cross between SHR-A3 and SHR-B2 revealed genetic variation on chromosome 17 responsible for higher systolic BP in SHR-A3. Congenic replacement of this locus in SHR-A3 results in systolic BP identical to SHR-B2 and partial amelioration in renal injury.[93] Genetically determined elevation of systolic BP beyond the autoregulatory range contributes to renal injury in SHR-A3.

Eng et al[94] used the 2 kidney-one clipped rat model in which hypertension is induced by reduction of blood flow in a single renal artery, resulting in elevated angiotensin II to uncover a link between hypertension and renal inflammation. The absence of injury in the clipped kidney that is partially protected from elevated BP, but experiences similar levels of angiotensin II as the unclipped kidney, indicated that injury was primarily driven by pressure. A predominant effect of pressure on renal injury was confirmed in angiotensin II or norepinephrine-induced hypertension in which one kidney was protected from increased pressure by a servo-controlled device in the renal artery.[95,96] These studies have been extended to determine whether recruitment of leukocytes into the kidney in hypertension is driven by angiotensin or pressure and reveal that it is increased perfusion pressure that drives leukocyte infiltration.[17] Induction of injury creates renal inflammation that is accompanied by release of cytokines from damaged tissue and leukocyte recruitment.[97–99] Leukocyte infiltration in response to pressure may be relevant to *APOL1*-induced renal injury in humans because leukocyte infiltration will promote cytokine upregulation of *APOL1* gene expression which in turn promotes glomerular injury.[48] Thus, immune mechanisms of hypertensive renal injury may be subject to genetic influences arising within immune cells recruited to the kidney.

SHR-A3 provides support for this concept. The immunoglobulin heavy chain (*Igh*) gene encodes B-cell receptors and secreted antibodies. *Igh* is extremely variable in both SNP and SV in mammals.[100–104] High diversity may reflect adaptations in a gene that has numerous segments (constant, joining, diversity, and variable) with substantial similarity. The expressed products of *Igh* are also diversified by immunoglobulin affinity maturation during B-cell development that arises by somatic hypermutation of *Igh* to increase antibody specificity and affinity.[105] Replacement of the *Igh* locus from SHR-A3 with the same locus from SHR-B2 curtails renal injury without affecting preinjury BP.[106] In SHR-A3 *Igh* contains variation that markedly increases serum levels of IgG2c and reduces IgG2b.[107] There is also extensive variation in the large part of the gene encoding *Igh* VDJ segments.[101] Immunoglobulins contribute, both directly and indirectly, to a wide range of CKD. The extensive *Igh* SNP and SV in humans is poorly addressed by SNP-based genotyping arrays and provides an illustration of the inability of SNP-GWAS studies to provide comprehensive genetic association studies.[100,108,109]

A third genetic variant driving renal injury in SHR-A3 affects T- and B-lymphocyte function (Figure 3). T- and B-cell receptor stimulation activates responses including cell proliferation and atrophy, cytokine production, and altered metabolic state that are mediated by Ca^{++} signaling. Stromal interaction molecule 1 (STIM1) protein gates entry of Ca^{++} into lymphocytes.[110–113] In SHR-A3 *Stim1* contains a premature stop codon producing a truncated protein and reducing Ca^{++} signaling.[114] Replacement of the defective *Stim1* allele in SHR-A3 remedies defective Ca^{++} signaling and substantially reduces renal injury without effect on preinjury BP.[114] Rare genetic defects in humans producing complete loss of *Stim1* function are associated with autoimmune disease attributable to disturbed antibody formation.[115,116] Thus, SHR-A3 has accumulated 2 gene variants with important consequences for antibody formation that drive renal injury in the presence of hypertension.

AGING, INFLAMM-AGING, AND AUTOREGULATION

CKD risk alleles coexist with nonheritable factors, such as increasing age, that compound with genetic predisposition.[117] Collectively, age-related diseases share pathogenic mechanisms including chronic sterile inflammation, called inflamm-aging.[118] Aging is associated with

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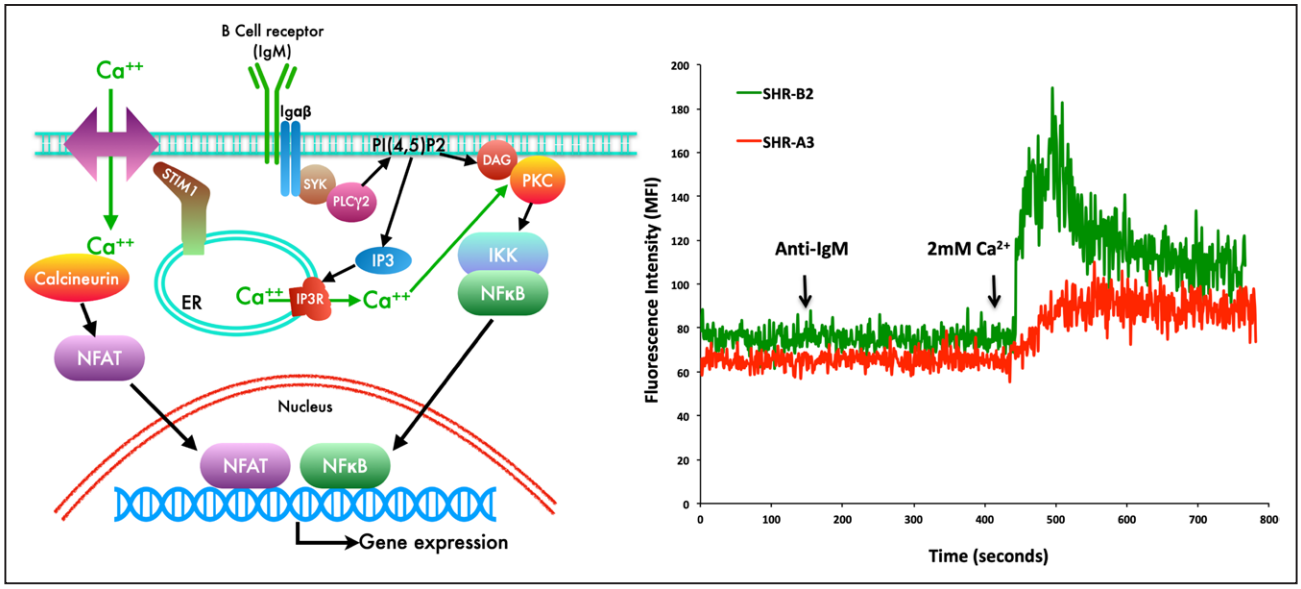

Figure 3. A mutation in stromal interation molecule 1 (*STIM1*) leads to defective calcium handling and altered B-cell receptor signaling in stroke-prone spontaneously hypertensive rats (SHR-A3).
Left, B-cell receptor signaling results from activation of the cell surface IgM receptor by antigen. PLCγ2 is activated to initiate inositol triphosphate (IP3) and diacyl glycerol (DAG) production. IP3 acts in the endoplasmic reticulum to allow release of stored Ca^{++} via the IP3 receptor. This calcium activates PKC (protein kinase C) with resulting activation of the IKK complex leading to the generation go NF-κB (nuclear factor-κB). Depletion of the ER calcium store activates Stim1 which then gates opening of the Orai1 Ca^{++} channel through which abundant extracellular calcium is able to enter the B cell. This large Ca^{++} signal is sufficient to activate calcineurin, a protein phosphatase that dephosphorylates NFAT. NFAT and NF-κB enter the nucleus and drive a complex set of transcriptionally mediated phenotypic changes by altering gene expression. **Right**, Mutation of Stim1 in renal injury-susceptible hypertensive rat line SHR-A3, but not in injury-resistant SHR-B2, alters calcium activation in the B cell. In SHR-A3, the COOH-terminal tail of Stim1 is absent due to the presence of a premature stop codon. This impairs the gating of Orai1. When B cells are placed in low Ca^{++} medium and activated by anti-IgM antibody cross linking of the B cell receptor, ER Ca^{++} stores are depleted and cannot be refilled. When extracellular Ca^{++} is subsequently increased to 2 mmol/L, the Orai1 mechanism in SHR-B2 is primed by Stim1 due to ER Ca^{++} depletion and a large flux of Ca^{++} entry ensues (store-operated calcium entry [SOCE]). In SHR-A3, the SOCE is strongly suppressed due to deficient interactions with Orai1 resulting from Stim1 mutation. Ca^{++} dependent activation of lymphocyte transcriptional responses is strongly impaired in SHR-A3.

increased levels of cytokines and chemokines.[119] Gene expression profiling reveals age-related altered immune functions in multiple organs[119] and tissue infiltration of lymphocytes is also observed.[120] Age differences in immune function reflect altered proliferative responses to continuous antigenic inputs that may require compromises between immune cell compartment size, stemness, and differentiation.[121] This occurs alongside impairment of memory cell generation due to negative regulatory programs compromising T-cell expansion.[121] Maladaptive B-cell responses in aging are revealed by deficient antibody responses to vaccination.[122] Aged B cells have impaired interactions with T cells that may impair immunoglobulin maturation,[122] altered transcription factor profiles,[123] and altered metabolic responses to stimulation.[124] Fibroblasts increase TNF (tumor necrosis factor)-α production with aging, and this may alter healing.[125] These changes mirror some of the genetic alterations in immune function discussed earlier, yielding aging phenotypes that echo and amplify genetic predisposition to immune dysfunction.

Studies seeking to find the genetic basis of variation in longevity in human centenarians have identified genes and pathways that include extensive involvement of immune genes operating in PKC (protein kinase C) and NF-κB (nuclear factor-κB) pathways central to immune cell function.[126] Interestingly, studies in model organisms have also identified similar genes and pathways in aging traits.[127–129] Thus, interaction may occur between genetic variation that drives aging and immune system function that affects the emergence and or progression of renal disease.

The aging kidney experiences reduced glomerular filtration,[130] renal blood flow, glomerular plasma flow rate, ultrafiltration coefficient, and glomerular hydraulic permeability.[131] These are often present in aging without kidney disease and suggest that age-indexing GFR might avoid skewing the definition of CKD.[132] Age-related changes in renal function have also been examined in rats. In the normotensive outbred Sprague-Dawley rat strain 90% of 24-month-old animals experience proteinuria and glomerular IgM accumulation indicating glomerular dysfunction.[133] Afferent arteriolar resistance is decreased in aged rats; consequently, glomerular perfusion pressure increases with rising albuminuria.[134]

The link between aging, hypertension, and renal injury may involve renal autoregulation. Normal autoregulation is impaired in aged mice compared with genetically

matched young animals.[135–137] In aged animals increased renal artery pressure resulted in increased renal blood flow, while younger animals were able to completely autoregulate blood flow.[135] The altered myogenic response in aged animals was reflected in reduction of pressure-induced intracellular calcium in the afferent arteriole. Autoregulatory capacity is also reduced in aging humans. Hill et al[138] proposed that defective autoregulation in aging humans as indicated by morphological correlation between focal dilated renal arterioles, hypertrophic glomeruli, and subsequent focal segmental glomerulosclerosis.

SUMMARY

Progressive renal disease in hypertension is complex with interaction between heritable and nonheritable elements. Phenotypic description of renal function in population-scale studies is constrained and likely limits GWAS success. GWAS is also limited by using SNP variants and is uninformed regarding other genomic variation, including SV, that contribute to phenotype diversity.[9,10] Undoubtedly, better understanding of the full scope of human genetic variation and tools for SV genotyping will advance genetic studies of CKD. Animal models have contributed additional insight, amplifying the role of genes critical to glomerular barrier formation and tubular reabsorption of filtered protein and indicating that genetic variation can affect autoregulation of renal blood flow. Pressure-induced renal injury initiates a chronic sterile inflammatory and immune response. Animal models have also indicated that genetic variation affecting immune responses can determine progression and severity of disease. While experimental gene knockout is useful only for defining the capacity of a gene to induce a renal phenotype, human CKD risk alleles may ultimately be reconstituted in animal models to demonstrate their effects and their interactions with other risk variants to yield polygenic animal models of greater usefulness. Finally, heritable influences contributing to renal injury may interact with aspects of normal aging to amplify the effects of elevated BP on disease.

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Disclosures

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