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Genes and Environment in Chronic Kidney Disease Hotspots

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Abstract

Purpose of Review: Chronic Kidney Disease (CKD) can cluster in geographic locations or in people of particular genetic ancestries. We explore APOL1 nephropathy and Balkan Nephropathy as examples of CKD clustering that illustrate genetics and environment conspiring to cause high rates of kidney disease. Unexplained hotspots of kidney disease in Asia and Central America are then considered from the perspective of potential gene x environment interactions.

Recent Findings: We report on evidence supporting both genes and environment in these CKD hotspots. Differing genetic susceptibility between populations and within populations may explain why causal environmental risk factors have been so hard to identify conclusively. Similarly, one cannot explain why these epidemics of kidney disease are happening now without invoking environmental changes.

Summary: Approaches to these CKD hotspots are of necessity becoming more holistic. Genetic studies may help us identify the environmental triggers by teaching us about disease biology and may empower environmental risk factor studies by allowing for stratification of study participants by genetic susceptibility.

Keywords

APOL1; Balkan Nephropathy; CKDu; Mesoamerican Nephropathy; gene environment interaction

Introduction

Rates of chronic kidney disease (CKD) vary widely by geography and ethnicity. Nephrologists have known for decades that some ethnic groups, such as African Americans, develop kidney failure more frequently than other groups living in the same regions. Peculiar patterns have emerged linking some regions with particular kidney phenotypes, such as the tubulointerstitial kidney disease that clusters in several Balkan countries, an observation made almost 70 years ago and perplexing investigators for 40 years until a combination of happenstance and exceptional detective work brought the etiology of disease into focus. These instances of kidney disease clustering likely have both genetic and environmental components, with environmental factors triggering disease in susceptible hosts. Multiple other kidney disease hotspots are challenging investigators with provocative clues regarding

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causality. Here we present several CKD hotspots around the globe, some partially understood and others where the cause remains elusive.

Genetics of CKD susceptibility

African Americans and other individuals of recent African ancestry develop end-stage kidney disease at 4-fold higher rates than Americans of European ancestry. The increased risk of CKD in African Americans can also be viewed as geographic clustering (Figure 1), which is the way we currently think about other CKD hotspots. Though this disparity has often been attributed to various environmental, socioeconomic, and traditional risk factors (such as diabetes), familial studies suggested that genetics could also be playing an important role.¹ The advent of the human genome project, powerful tools such as genome-wide genotyping arrays, and catalogs of human diversity such as HapMap in the 2000's allowed investigators to test genetic hypotheses about kidney disease risk. A major breakthrough involved the use of genetic admixture studies. These studies took advantage of mixed African and European ancestry in African Americans to locate chromosomal regions from the high risk (African) background in kidney disease cases vs. controls, identifying a very strong locus on chromosome 22.^{2, 3} Subsequently, coding variants in the APOL1 gene were identified as the causal variants at the chromosome 22 locus and were shown to account for a large fraction of this risk difference.⁴⁻⁶

African Americans with two APOL1 risk alleles (one inherited from each parent) have a 3–30 fold increase in risk for a variety of non-diabetic kidney diseases compared to African Americans with zero or 1 risk allele(s). These APOL1-associated diseases include hypertension-associated ESKD (H-ESKD), focal and segmental glomerulosclerosis (FSGS), HIV nephropathy (HIVAN), and other phenotypes that include collapsing glomerulopathies.^{4, 5, 7–10} These APOL1 risk variants have been observed exclusively in individuals with recent African ancestry. The risk alleles arose approximately 5,000 years ago in sub-Saharan Africa, long after the out-of-Africa population expansions that peopled Asia and Europe, explaining why they are not present in non-African genomes.¹¹ Both population genetic and experimental laboratory evidence strongly support the idea that the APOL1 kidney risk alleles offer more protection against African sleeping sickness than wild-type APOL1 alleles.^{4, 12, 13} Whereas one risk allele appears to protect against trypanosomal disease, two risk alleles have a major impact on kidney failure rates in both the United States and Africa.

Though the mechanism of disease by which risk variant APOL1 causes kidney disease is far from clear, the fundamental susceptibility caused by APOL1 has been validated in numerous studies. However, the APOL1 risk alleles do not cause Mendelian disease, and most individuals with the high-risk APOL1 genotype do not develop kidney disease. A second hit is required, and though one genetic modifier has been identified and replicated for FSGS, to date there is more evidence that these additional factors are environmental rather than genetic, at least for the common form (H-ESKD) of APOL1 kidney disease.^{14, 15} One important and powerful environmental factor has been defined: HIV infection.^{7, 16} Investigators estimate that fifty percent of individuals with the APOL1 high-risk genotype infected with HIV developed the aggressive glomerular lesions characterized by HIVAN prior to the widespread use of highly-active antiviral therapies. Today, HIV is a rare cause of

APOL1 kidney disease, at least in the United States, though it remains a significant challenge in Africa. The other environmental factors that trigger APOL1 kidney disease remain largely unknown. Now that we can stratify individuals by APOL1 genotype, we can begin asking what these triggers of disease might be, comparing individuals who carry the high risk genotype with and without disease (Figure 2). Other viral infections beside HIV, as well as the anti-viral cytokine interferon, both likely play a role in initiating the disease process.^{8,17, 18}

Another example of an important kidney disease with a geographic and ethnic predisposition is IgA nephropathy. This entity occurs most commonly in Asia and individuals of East Asian ancestry develop IgA nephropathy more frequently than other groups even when residing outside Asia. Genetic association studies have demonstrated many common genetic variants linked to IgA nephropathy, with the risk variants tending to be more common in Asians.¹⁹ The risk variants are located in or near many genes important for the innate immune system, enriched for genes important for host defense against parasites in the helminth family.²⁰ In this instance, genetic diversity that enhanced human resistance to helminthes may have engendered susceptibility to inflammatory kidney disease. Environment likely shaped genetic susceptibility, and though the role of environment in triggering disease today is not entirely clear, the common pattern of IgA nephropathy development and subsequent flare-ups shortly after upper respiratory and other infections does point toward potentially important environmental triggers.

Other common genetic variants associated with CKD likely cause differential susceptibility to CKD primarily within populations. The locus most consistently associated with CKD in genetic association studies is UMOD.^{21–24} UMOD encodes for Tamm-Horsfall protein (THP), an abundant protein in normal human urine. A substantial body of evidence indicates that THP is protective against both urinary tract pathogens and kidney stones.^{25, 26} Genetic variants in UMOD that strongly associate with CKD are also expression quantitative trait loci, meaning that SNPs that increase risk of CKD also raise expression of UMOD.²⁶ One set of CKD-associated SNPs appeared in some discrete geographic location in the distant past and then spread globally, rising in allele frequency to ~80% in humans worldwide, strongly suggesting an allele frequency sweep due to natural selection, perhaps by protecting against urinary tract pathogens.¹¹

As a group, these examples illustrate that genetic variants can be adaptive in certain environmental conditions but be very maladaptive in others. An emerging theme is that genetic risk variants conferring more robust innate immunity against pathogens may also predispose to kidney disease, and that pathogens may trigger these innate immune pathways in a way that leads to deleterious consequences. They highlight the complexities of gene-environment interactions in causing disease, but also suggest that ancestry and human migrations from one environment to another may partly explain the heterogeneity in the prevalence of CKD worldwide.

Environmental causes of CKD clustering

A clustering of kidney disease was first described in Bulgaria in the 1950's, with high prevalence rates later discovered to extend through parts of what are now Serbia, Croatia, Romania, Bulgaria, Bosnia, and Herzegovina.²⁷ Geographical regions affected by the disease are patchy in nature. The phenotype is characterized by slowly progressive kidney disease that appears in middle age and is frequently associated with upper urothelial cancers. This kidney disease came to be known as Balkan Nephropathy (BN). Investigators have pursued many hypotheses regarding etiology, including metals, microbial products (Ochratoxin), chemicals from coal deposits, aristolochia plants, and many others. It was the combination of CKD plus urothelial cancer that led investigators to make the connection with an outbreak of CKD with associated urothelial cancers in a weight loss clinic in Belgium in the 1990's where women had been treated with a cocktail of herbs that accidentally included aristolochic acid (AA).²⁸ Subsequently, using innovative molecular techniques, investigators were able to demonstrate AA-DNA adducts from kidney tissue and tumors from patients with BN, and also identified a set of p53 mutations that were very strongly associated with aristolochia exposure.²⁸ Today, the prevailing hypothesis is that AA is the causative agent of BN, with the degree of suspicion being high enough that "AA nephropathy" has replaced BN by many clinicians and investigators. It is believed that AA enters the food supply when it is incidentally harvested with wheat and milled into bread. Though alternative hypotheses are still championed by some investigators, the combination of epidemiology and molecular evidence make a strong case for AA, demonstrating the power of orthogonal approaches and molecular evidence in helping to move from epidemiologic association to causation. BN may be merely the tip of the iceberg with respect to AA nephropathy, as it has been estimated that millions of individuals in East Asia use AA as an herbal supplement.²⁹ CKD with or without urothelial cancers is proving surprisingly common in some of these Asian countries in recent studies.

While the major risk factor for BN is environmental, investigators had long observed that BN clusters in families and that some ethnic groups appear more susceptible to BN than others.³⁰ Many genetic studies have focused on genes that either may activate or detoxify AA based on biochemical studies of AA metabolism.³¹ The genes encoding the many enzymes that detoxify potentially harmful dietary constituents are among the most polymorphic in the human genome, with many low-functioning or null alleles that differ in frequency between populations. Many studies have attempted to elucidate genetic variation associated with BN, though these tend to be older candidate gene rather than non-hypothesis based approaches. While there are no genetic variants associated with BN at genome-wide levels of statistical significance, it is highly likely that humans differ in their ability to detoxify AA and also have differing susceptibility to AA-induced kidney injury. Though some people argue against the urgency of genetic studies to identify susceptibility alleles given that a probable cause has for BN has been identified, gene x environment studies might illuminate why only about 5% of the at-risk population develops BN and perhaps change dietary or other habits for those at highest risk.

Millions of patients with CKD have no etiologic diagnosis for their disease. Given that the kidney concentrates environmental toxins, both natural and manmade, exposure of kidney

tissue is often dramatically higher than other organ systems. Studies of extreme clustering of CKD have revealed many toxin-related epidemics including poisoning by cadmium, lead, melamine, and others. More widespread exposures such as several ubiquitous agrichemicals now used worldwide may be harder to conclusively demonstrate as contributing to CKD. Molecular studies may be the best way to identify important environmental toxins. Defining susceptible populations with genetics and fingerprinting the specific effect of individual toxins with epigenetic studies may prove crucial this process.

Approaching other foci of CKD clustering

Investigators have identified multiple hotspots of chronic kidney disease around the world not associated with common risk factors such as diabetes or antecedent hypertension. These sites of unusually high CKD prevalence have engendered the name “CKDu” (CKD of unknown etiology) to describe a group of possibly related diseases with shared elements but also important differences in both exposure profile and phenotype. Many provocative hypotheses have been proposed and supported by intriguing association data, but in each case the cause ultimately remains unproven. One can speculate about whether these hotspots are primarily environmental with possible underlying genetic susceptibility like BN or primarily genetic with one or more environmental triggers (that may result in a spectrum of phenotypes) like APOL1 kidney disease. Here, we focus on CKDu hotspots that share the characteristic of occurring most prominently in manual laborers who work in hot climates, principally in agricultural communities. It is worth considering why one worker gets disease while another with near identical exposures does not, but also what has changed in the environment such that the epidemics of kidney disease are happening now.

CKDu in Sri Lanka

Sri Lanka has been recognized as a CKDu hotspot since the 1990's.^{32, 33} The disease prevalence is highest among farmers in the North Central province. The Sri Lanka CKDu entity is referred to by many as CINAC (chronic interstitial nephritis of agricultural communities) to emphasize the strong connection to agricultural work. In contrast to some other CKDu hotspots, CKDu in Sri Lanka does not occur at high rates in coastal regions and it is not the hottest regions that are most affected. Reports document CKD rates of >20% in some provinces with relatively balanced male:female ratios.^{32, 34} In endemic regions, it is typical for 70–85% of CKD cases to have no clear etiology, whereas in nonendemic regions the rate of CKD without a diagnosis are often <10%.³⁵ Epidemiology studies to date have found more evidence to suggest a role for toxins, both elemental and agrichemical, than for heat stress or infectious causes.^{36, 37} In particular, investigators have put forth evidence for cadmium, arsenic, fluoride, numerous agrichemicals (particularly glyphosate, or Round-Up), and other candidates as the causal entity, though the data is frequently inconsistent or even contradictory.^{38,32} Glyphosate has come under intense scrutiny as a potential kidney toxin in Sri Lanka, with a possible potentiating effect of hard water due to high calcium levels, leading to a ban on glyphosate in 2015 that was subsequently lifted.³⁹

Toxins are a particularly vexing candidate to study. High levels of various toxins have been documented in some studies in CKDu patients vs. controls, but it is difficult to discern

whether the toxins cause CKDu or are just present at higher levels due to reduced clearance in study participants with disease compared to controls. There are almost certainly important individual differences in the absorption, detoxification, and clearance of toxins and also differences in susceptibility of tissue to injury from toxins. Family history has consistently been associated with CKDu in Sri Lanka in many studies, suggesting but not proving a heritable component, and hinting at a gene-environment interaction.^{35, 40–42} A GWAS was performed on 311 cases and 286 controls, and one locus was identified at genome-wide significance thresholds near a gene called SLC13A3. This gene encodes a dicarboxylate transporter expressed in kidney tubules that has been posited to have a role in xenobiotic secretion.⁴³ Unlike most genetic variants associated with common complex diseases where odds ratios are relatively small, the effect size of this variant is ~2 per allele, indicating a large increase in risk when comparing individuals with two risk alleles to those with zero risk alleles. Replication of the SLC13A3 locus would further support the idea of an ingested toxin as a causal agent in a biologically plausible gene-environment interaction. It would also potentially allow stratification by genotype and possibly provide additional power for environmental factor studies. Additional exome studies by the same investigators have provided some preliminary evidence for risk variants in a gene called KCNA10, a voltage-gated potassium channel, though the potential role for this gene in CKDu is not immediately clear.⁴⁴

CKDu in India

Another CKDu hotspot has been identified in the southeastern region of Andhra Pradesh.^{33, 45} Though CKDu in this region has been less intensively studied than other sites with high CKDu prevalence, the disease in India also chiefly affects farmers, with agrichemicals, heat stress, and metals as the prime suspects. The possibility of toxin-related gene-environment interactions has prompted candidate gene studies. Though not performed in the highest risk region, investigators in Northern India conducted case-control genetic studies for a similar phenotype with unexplained kidney disease.⁴⁶ They tested variation in the p450 gene CYP1A1 for relative frequency in CKDu cases vs age and sex matched healthy controls. This gene has several functional variants with higher allele frequency in Asians that may lead to higher levels of enzyme. The investigators postulated that toxins and/or agrichemicals were inducing this enzyme more robustly in risk variant carriers, leading to reactive oxygen species generation by CYP1A1 and promoting kidney injury. They reported an association between CKDu and variants with highest frequency in Asians with odds ratios ~2.

In another study, the same investigators considered the role of organochlorine pesticides (OCP), the glutathione-conjugating enzymes GSTT1 and GSTM1, and the interdependence between these potential environmental and genetic factors in CKDu.⁴⁷ OCPs have been shown to damage kidney cells in experimental systems, and GSST1 and GSTM1 help metabolize and excrete toxins. They reported increased OCP levels in CKDu patients compared with controls, higher frequencies of common GSST1 and GSTM1 null alleles in cases, and a measurable effect of these genotypes on OCP levels in regression models.

These hypothesis-based studies ask logical questions based on environmental exposure patterns and recognition of the large effect evolution has had on xenobiotic metabolizing enzymes. Replication is extremely important in this type of study, which tend to have low replication rates and over time are being replaced by genome wide non-hypothesis based approaches. In addition, studying genetic variants with substantial variability between populations may drive differences due to population stratification rather than direct effects of specific variants. Follow up studies in these populations with updated genetic tools may be very illuminating. Rapidly decreasing costs associated with genome-wide genotyping may make genome-wide genetic studies feasible in a wider range of research environments.

Mesoamerican Nephropathy, a CKDu epidemic in Central America

Kidney disease rates in Nicaragua and El Salvador are the highest in the Western hemisphere, about ten times higher than the United States. Within these countries there are hotspots where very high prevalence rates of CKD, sometimes in excess of 40%, have been observed.^{33, 48, 49} First documented in El Salvador in the 1990's, a majority of the ESRD patients had no etiologic diagnosis for their kidney disease.⁵⁰ The most remarkable clustering has since been observed in Northwest Nicaragua and the Bajo Lempa region of El Salvador, but high rates have also been seen in Honduras, Guatemala, Costa Rica, Mexico, and Panama. Now known as Mesoamerican Nephropathy, this discontinuous chain of CKDu hotspots occurs most visibly in agricultural workers, but reports also identify brick makers, miners, and port workers as other groups at high risk. Traditional risk factors such as diabetes, hypertension, and obesity tend to be relatively low in most of these occupational groups. Agrichemicals, heat stress, infectious agents, and metals have been studied without conclusive results, though most experts favor an occupational exposure, in part supported by the very high male:female ratio of observed disease. Potential evidence for early renal injury has been documented in children.⁵¹ Hard manual labor in high heat is one common thread connecting populations with high disease rates. It remains hard to explain why many other regions with hot climates and similar work environments do not have similarly high rates of kidney disease, or why some workers develop disease after only a few years while others have preserved kidney function after decades, without invoking individual differences in susceptibility. Both population level and within-population genetic variation may underlie these observations, whether the predominant risk factor is heat or not. Recent field observations have supported roles for recurrent acute kidney injury,^{52, 53} febrile illness preceding renal function decline,^{52, 54, 55} and elevated rates in specific job categories (particularly sugarcane cutters).^{53, 55, 56, 48, 57, 58} Additional suspicion has fallen on uric acid and pathogens known to cause kidney injury such as leptospira.^{58–61}

It is notable that all the most severe and best documented hotspots of MeN occur on the Pacific Coast of Central America. The fact that CKD rates decline with increasing altitude and distance from the coast in some studies may support a local environmental factor, but the absence of well-documented hotspots on the Caribbean coast is worthy of mention. The Pacific coast MeN hotspots occur in regions with a complex admixed population of mostly Native American and European ancestry, with a lesser contribution of African ancestry. This contrasts with the Caribbean coast where African ancestry predominates. Though important differences exist in work practices between sugarcane work in MeN hotspots and Caribbean

sugarcane production sites, high CKD rates have not been observed in these latter groups of workers composed of individuals of primarily African ancestry.³⁷ Recent studies of sugarcane workers in Africa also have not demonstrated high rates of kidney disease, albeit again with potentially meaningful differences in the environment.⁶² The stark differences in CKDu rates suggest that genetic studies may add an important dimension to MeN studies.

Natural selection drives populations to adapt to local environments, causing beneficial alleles to rise in frequency and detrimental alleles to become scarcer. The highly admixed Central American population has resulted from movements of people and shuffling of genomes in a new environment. It is interesting to consider how the journeys of people even thousands of years ago may have affected the genomes of their ancestors. One can speculate about the effects of what living in Arctic climates for thousands of years during the migration from Siberia to North America had on the genomes of Native American populations, particularly with respect to the processes of heat conservation and pathogen defense, and how these changes might affect physiological function in current tropical environments. Genetic studies are in progress and speculation may be replaced by specific variants that could clarify the nature of susceptibility and triggers in MeN.

Investigators have also employed animal models to explore potential MeN causal factors. A series of papers has used mouse models to consider the roles of heat stress and repetitive kidney injury, and the influence of the uric acid, fructose metabolism, hyperosmolality, and the polyol pathway.^{63–65} This work has provided evidence that many of the hypotheses derived from epidemiology studies are biologically plausible.

Conclusion: Untangling the mysteries of CKDu hotspots

Common complex diseases such as diabetes, hypertension, or CKD by definition have both genetic and environmental risk factors. Clustering of disease, as happens in CKDu, suggests an unusually strong contribution from either genetics, environment, or both. These hotspots likely represent the locations where genetic susceptibility and environmental triggers share the most overlap. The hope for solving these multifactorial problems is buoyed by the examples of progress on some dizzyingly complex biological systems such as the interactions of gliadin (wheat protein) consumption, genetics (most prominently HLA locus), and Reovirus infection on development Celiac Sprue.⁶⁶

At the molecular level, the epigenome is where genetics and environment intersect. Here, epigenetics might be most productively thought of not just as heritable changes to DNA caused by the environment but also to include the more permissive definition of effect of environment on gene expression. Tools to study the epigenome lag far behind modern genomics/genetics but are nonetheless advancing steadily. Access to disease-relevant tissue remains a high hurdle when the organ is difficult to sample, especially since advanced kidney disease itself can alter the cellular environment in ways that makes observing early inciting factors difficult. The identification of AA-DNA adducts was a critical piece of the BN puzzle, but required a high level of suspicion from epidemiologic studies to justify the investment in laborious hypothesis-based molecular studies. The ability to sample the methylome, or methylation events across the genome, represents an important advance in

considering exposures. The ability to “fingerprint” the genome or proteome for a huge array of exposures would seem like a far-off goal, but perhaps no more so than obtaining the human genome sequence once did.

Studying CKDu hotspots invariably involves breaking down a hugely complex problem into a series of manageable sub-problems. Defining genetic susceptibility may be one such tractable problem. It would allow us to compare people with high genetic susceptibility who do and do not have disease for specific environmental exposures. The genetic variants may themselves give us valuable clues about the potential environmental triggers. The one-way causality arrow between genotype (fixed at birth) and phenotype makes data interpretation more manageable in some instances than trying to understand the directionality of causation between environmental factors and phenotype (e.g. does a toxin cause CKD or does CKD lead to measuring high levels of a toxin?). Embracing new technologies is also essential to study environmental risk factors, such as bracelets that can sample the environment and be interrogated for thousands of compounds, or satellite mapping of potential elemental toxins from space to compare with disease clusters. Interdisciplinary collaborations would seem critical. And nothing will replace old-fashioned, relentless detective work.

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- *Zhang: This paper reports the first replicated genetic variants that modify the APOL1 risk variants in FSGS.*Langfeld: A survey for strong modifiers of the common form of APOL1 nephropathy, hypertension-associated ESKD, did not find any individual genetic modifiers of large effect size, suggesting that environmental factors are probably the critical second hit in most cases.**Cooper: The authors use population-based studies to explain why the APOL1 high risk alleles are most common in West African when the pathogen they had been presumed to protect against (*T. brucei rhodesiense*) are present mostly East of the Rift Valley. Specifically, they identify a role for the G1 risk allele in preventing aggressive disease caused by *T. Brucei gambiense*, a pathogen dispersed widely in West Africa. This is the latest installment in a fascinating story that details how events that happened in the distant past can influence kidney disease rates in today's populations.*Chang: This paper adds support to the developing idea that viruses and interferons may be important second hits in APOL1 kidney disease.*Herath: The authors make their case against the increasingly popular hypothesis that heat stress is an important element linking several CKD hotspots around the world.*Fischer: Fischer and colleagues report on a cohort of Central American sugarcane workers who developed fever and acute kidney injury, and had findings suggestive of interstitial nephritis on kidney biopsy. They call attention to both the possible roles repetitive acute kidney injury and infectious causes in Mesoamerican Nephropathy.**Bouziat: A remarkable story that begins to untangle the gene x environment complexities of Celiac Sprue. We have known

about many of the susceptibility genes and the dietary trigger. Now, reovirus infection represents the plausible “switch” from susceptibility to disease.

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Key points:

1. APOL1 nephropathy is a paradigmatic example of a genetic disease with important environmental triggers.
2. Balkan nephropathy is best thought of as an environmental disease (Aristolochic Acid ingestion) that likely has important genetic susceptibility factors.
3. CKD hotspots in general likely occur where genetic susceptibility and environmental triggers share significant overlap.
4. Unsolved CKD hotspots with likely important genetic and environmental influences include Sri Lanka, Central America, and India.

Figure 1. Kidney Disease in African Americans: a “hotspot” caused by genetic susceptibility. Percentage of African Americans by state in the United States (*CensusScope*: www.censusscope.org). A strong correlation exists between rates of kidney disease and African American ancestry. Genetic variation in the APOL1 gene explains a large fraction of this disparity in kidney disease rates. Despite the very large risk of kidney disease conferred by the APOL1 risk alleles, most individuals with the high risk genotype do not develop kidney disease, suggesting that environmental triggers are also required.

Figure 2. Defining genetic susceptibility in a CKD hotspot may make studies of environmental risk factors more powerful.

(top) Picture a population with very high rates of kidney disease. On the left hand side are disease cases and the right hand side are controls. The yellow spurs indicate individuals exposed to a particular environmental risk factor of interest. There appears to be some excess of exposures in the cases, but the data are not conclusive. (middle) A genetic study defines the genetically susceptible population. This could be either due to penetrant risk alleles at a single genetic locus or by an array of risk alleles, each of modest power, where the aggregate risk can be expressed in the form of a high polygenic risk score. (bottom) The overlap of genetic susceptibility and specific environmental exposure is illuminating. By comparing only susceptible cases with susceptible controls, strong differences in exposure to a putative environmental risk factor may become evident.