APOL1 Nephropathy: A Population Genetics and Evolutionary Medicine Detective Story

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Summary: Common DNA sequence variants rarely have a high-risk association with a common disease. When such associations do occur, evolutionary forces must be sought, such as in the association of apolipoprotein L1 (*APOL1*) gene risk variants with nondiabetic kidney diseases in populations of African ancestry. The variants originated in West Africa and provided pathogenic resistance in the heterozygous state that led to high allele frequencies owing to an adaptive evolutionary selective sweep. However, the homozygous state is disadvantageous and is associated with a markedly increased risk of a spectrum of kidney diseases encompassing hypertension-attributed kidney disease, focal segmental glomerulosclerosis, human immunodeficiency virus nephropathy, sickle cell nephropathy, and progressive lupus nephritis. This scientific success story emerged with the help of the tools developed over the past 2 decades in human genome sequencing and population genomic databases. In this introductory article to a timely issue dedicated to illuminating progress in this area, we describe this unique population genetics and evolutionary medicine detective story. We emphasize the paradox of the inheritance mode, the missing heritability, and unresolved associations, including cardiovascular risk and diabetic nephropathy. We also highlight how genetic epidemiology elucidates mechanisms and how the principles of evolution can be used to unravel conserved pathways affected by APOL1 that may lead to novel therapies. The *APOL1* gene provides a compelling example of a common variant association with common forms of nondiabetic kidney disease occurring in a continental population isolate with subsequent global admixture. Scientific collaboration using multiple experimental model systems and approaches should further clarify pathomechanisms further, leading to novel therapies.

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Chronic kidney disease (CKD) affects approximately 7% of the population worldwide across all stages of kidney disease.[1] The decreasing prevalence of progressive stages of declining glomerular filtration rate (GFR) is thought to reflect the cruel censoring effect of cardiovascular mortality as a complication observed even in early stages of CKD.[2–4] In the United States, the prevalence ratio of CKD to end-stage kidney disease (ESKD) is approximately 50 to 1,[5] consistent with this censoring effect. Thus, death from CKD is not primarily owing to the reduction of GFR to a level incompatible with life, but rather to the poorly understood effect of kidney injury on the cardiovascular system.[2–4]

The burden of progressive CKD is not distributed proportionately across global population groups.[1] Populations of sub-Saharan African ancestry experience an approximately 4-fold higher prevalence of ESKD.[6] This distribution has been documented best in US-based surveys comparing the burden of kidney disease in the African American community with that of other populations.[6] These studies have shown that the disparities apply to both diabetic and nondiabetic kidney disease, with the most striking disparity observed in the latter, particularly in young adults.[7] The estimated lifetime risk for the development of ESKD approaches 8% among individuals of recent African ancestry, whereas the risk among individuals of European ancestry is 2% to 3%.[8] The likelihood of developing ESKD is at least 50 times greater among African American patients infected with human immunodeficiency virus (HIV) than among European Americans with HIV.[9,10]

All human populations are of African origin, with migration out of Africa accounting for colonization of all other continents during the past more than 100,000 years. The expression *recent African ancestry* refers to indigenous contemporary continental African populations and descendants who left continental Africa under the tragic human slave trade within the past several centuries. African Americans represent one of the most prominent of such populations. Underlying these statistics are the numerous stories of individual human suffering frequently encountered by nephrology

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health care professionals caring for African American patients with CKD. These patients often speak of the many family members who have died of CKD and its complications, but without a clear monogenic inheritance pattern. This non-monogenic pattern of familial clustering has been well documented.[11,12] Socioeconomic factors contribute to the increased kidney disease risk and its devastating consequences. As reportedly stated by Dr. Martin Luther King Jr. on March 25, 1966, at the second convention of the Medical Committee for Human Rights in Chicago, IL: "Of all the forms of inequality, injustice in health is the most shocking and inhuman." Although lower socioeconomic status and poor access to health care explain a portion of the kidney disease risk,[13–16] genetic factors are also a significant contributor.[11,12,17]

THE DISCOVERY OF AFRICAN KIDNEY RISK GENETIC LOCI BY ADMIXTURE LINKAGE DISEQUILIBRIUM MAPPING

Two overall approaches can be used to discover disease-causing genetic loci: family based disease gene discovery, which was conducted previously using linkage and now is performed by whole-exome and whole-genome sequencing[18]; and population-based disease gene discovery, among which the most widely used methodology is genome-wide association studies (GWAS).[19,20] Family based discovery has failed to identify genes that explain the overall heritable component of the disparity in CKD in populations of recent African ancestry because the penetrance is too low for Mendelian segregation. However, at the population level, in seminal publications, two groups reported the results of a modified version of a GWAS to identify a genomic region containing risk variants strongly linked to ESKD risk loci.[21,22] This modified approach is termed *mapping by admixture linkage disequilibrium* (MALD).[23–25] Linkage disequilibrium (LD) refers to the nonrandom association of alleles at different loci. Loci are said to be in linkage disequilibrium when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly. In classic GWAS, only genetic markers with sufficient physical proximity to a true disease risk–causative variant to mitigate recombination are associated with the disease risk phenotype of interest (Fig. 1). MALD is suitable for population-based discovery of disease risk alleles in admixed populations with a strong genetic locus variant underlying a large difference in disease susceptibility between the parent populations comprising the admixture (Table 1). The basic principle of MALD relies on genotyping the small proportion of genetic variants that differ in frequency across populations of

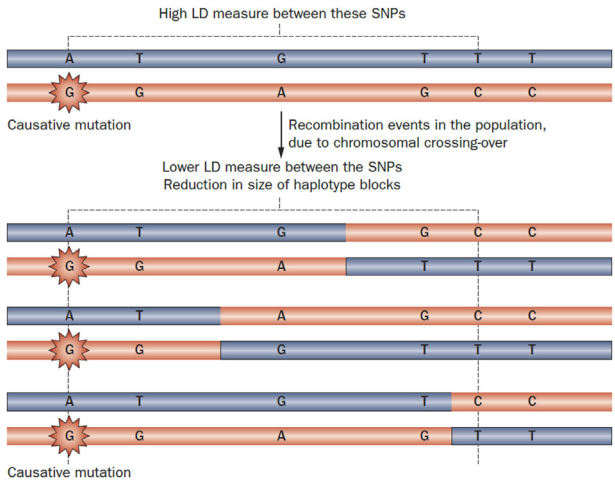

Figure 1. Linkage disequilibrium breakdown and admixture. The effect of recombination on linkage disequilibrium and haplotype blocks. When a mutation arises in a population, it is associated initially with neighboring SNPs, which are transmitted as a haplotype (high linkage disequilibrium). If such a mutation is causative of disease, then SNPs in the region can be used as markers of its presence. These SNPs usually maintain a strong statistical association with the disease phenotype of interest. As the mutation spreads within a population, recombination occurs with the passage of generations and linkage disequilibrium breaks down, shrinking the size of the initial haplotype block and, in the process, creating new haplotypes. In this figure, two initial haplotypes (top), which are marked by six SNPs, give rise to six different haplotypes in the population (bottom). Reprinted with permission from Rosset et al.[91]

different ancestries.[26] When abrupt recent admixture occurs between populations that had been separated previously by geographic or other boundaries, the resulting admixed population inherits large blocks of chromosomal regions of one ancestry or the other. These regions can be identified by genotyping markers that show substantially different allele frequencies between ancestral or parental populations (Fig. 2). This admixture-generated LD enables linkage-based disease gene discovery in GWAS, with the ability to calculate logarithm of odds scores for large regions that usually contain many dozens of genomic loci.

By using a MALD approach, two groups identified the genomic region enriched in African ancestry single-nucleotide polymorphic (SNP) markers among individuals with kidney disease compared with healthy African American controls and their genome-wide average.[21,22] The highest single-point logarithm of odds score was detected on chromosome 22 for the nondiabetic ESKD analysis. The initial analysis suggested that multiple SNPs in the *MYH9* gene account for the admixture-generated signal in this region.[21,22,27] Two of these intronic mutations in *MYH9* were predicted to modify splice-determining motifs.[28] However, none of the SNPs in *MYH9* influenced transcription, translation, or protein function directly, and further studies failed to show causality. The inability to show causality coupled with the identification of a

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