

IN THE LITERATURE

The Genetic Basis of Kidney Disease Risk in African Americans: *MYH9* as a New Candidate Gene

Commentary on Kopp JB, Smith MW, Nelson GW, et al: *MYH9* is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 40:1175-1184, 2008 and Kao WH, Klag MJ, Meoni LA, et al: *MYH9* is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet* 40:1185-1192, 2008.

Chronic kidney disease (CKD) is a complex genetic disorder. Familial aggregation of both diabetic and nondiabetic kidney disease is known¹⁻³ and traits such as glomerular filtration rate and albuminuria are highly heritable.⁴⁻⁷ Aggregation of CKD by race adds a further dimension to its genetic basis, suggesting gene flow from separate ancestral gene pools. The markedly exaggerated risk of CKD in the African American population of the United States has been appreciated for several decades. In 2006, the US Renal Data System documented rates of treated kidney failure (end-stage renal disease [ESRD]) that were 3.6-fold greater in African Americans than whites.⁸ Although African Americans have the highest rates of hypertension and the second highest rates of diabetes prevalence among ethnic groups in the United States,^{9,10} increased prevalence of these primary diseases is insufficient to explain the excess risk of CKD.^{11,12} While socioeconomic status, lifestyle factors, and clinical factors such as hypertension and diabetes could contribute to as much as 40% of the excess risk,¹³ African Americans still carry a nearly 2-fold greater risk of CKD relative to the white population.^{13,14} The increased risk extends to kidney disease of several etiologies including diabetic nephropathy,¹⁵ hypertensive kidney disease,¹⁶ lupus nephritis,¹⁷ focal segmental sclerosis (FSGS),¹⁸ HIV-associated nephropathy (HIVAN),¹⁹ and glomerulonephritis.²⁰ It encompasses both an increased susceptibility to CKD,¹⁶ as well as a more rapid progression to ESRD.²¹

Both quantitative linkage approaches and genetic association studies have been applied to identify disease genes for CKD with limited success.²² Association studies provide a powerful strategy to uncover multiple genes with smaller effects. However a serious weakness is the propensity to false-positive results from genetic differences related to population substructure or admixture, especially if the prevalence of disease also differs in the component popula-

tions. Self-reported race may be associated with cryptic population stratification, making replication of study results in confirmatory investigations more challenging.²³ The gene pool of African Americans residing in the United States reflects the mixing of the native Africans, mainly from Western Africa, with European and Native American peoples, and has about 10% to 20% European admixture.²⁴ Minority populations have often been underrepresented in genetic association studies.

Two independent studies in the October 2008 issue of *Nature Genetics*^{25,26} successfully exploit the genetic architecture of population admixture in African Americans, using an analytic strategy called "mapping by admixture linkage disequilibrium" or MALD²⁷⁻²⁹ to detect a gene conferring increased risk for FSGS and for ESRD in nondiabetic individuals. To understand the findings in these manuscripts, 2 important concepts need to be explained. The first is admixture, which refers to the formation of a new population by interbreeding between individuals from genetically divergent parental populations. The second is linkage disequilibrium (LD), which describes the co-occurrence of 2 alleles at different loci on the same chromosome more often than would be predicted by random chance and is a measure of cosegregation of alleles in a population. MALD is especially appropriate to the study of diseases that differ in frequency between ethnic groups and requires recent admixture, measurable differences in the frequency of disease-causing alleles between parental populations, and a set of ancestry-informative markers

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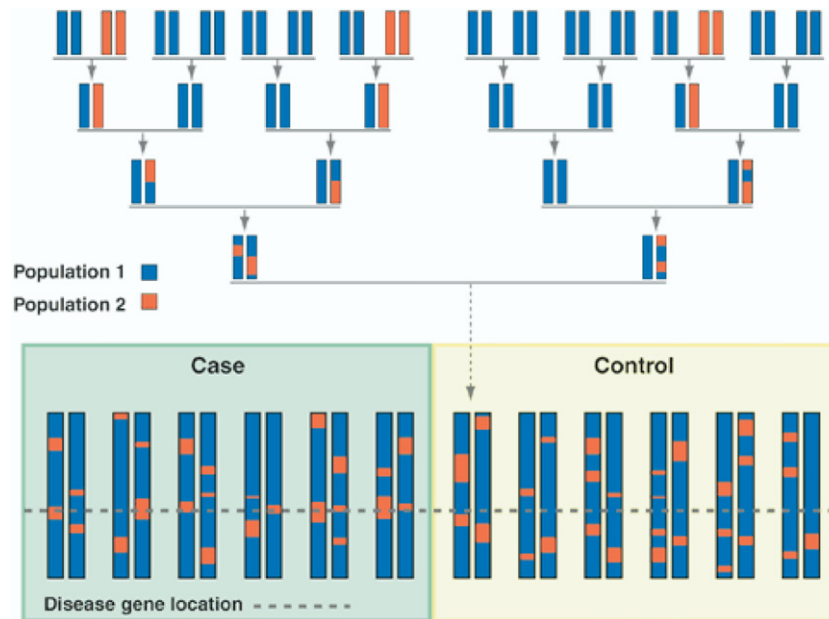


Figure 1. Schematic of 1 chromosome pair from each of several individuals in an admixed population. A group of cases (for a given disease) and a group of controls are presented at the bottom left and the bottom right, respectively. For one of the control individuals (arrow), a schematic of all ancestors in the last 4 generations is shown in the upper part of the figure. In the first generation, mixing between population 1 (blue) and population 2 (red) occurs, generating offspring with red- and blue-origin chromosomes; in later generations, crossing over during meiotic recombination creates red/blue chimeric chromosomes. Admixture mapping can be ideally applied if populations 1 and 2 carry a different allele at the disease locus (dashed line). Whole-genome scanning under the admixture mapping strategy consists of scanning the genome and identifying the regions with an excess of “red” ancestry in the cases versus the controls, assuming that the “red” population carries the predisposition allele. Reproduced from Darvasi and Shifman²⁹ with permission.

that specifically differentiate chromosomes derived from the parental populations based on allele frequency differences between the populations. MALD takes advantage of LD between genetic ancestry marker alleles and disease alleles (Fig 1); because of recent admixture, such LD may be seen over long chromosomal segments with the advantage that fewer markers can be used for a genome search than other methods of association mapping.

WHAT DO THESE IMPORTANT STUDIES SHOW?

The studies by Kopp et al and Kao et al in *Nature Genetics* identify variation at *MYH9*, a gene on chromosome 22, as a major risk factor for FSGS and nondiabetic kidney disease in African Americans. Their approach, using admixture mapping, identifies the strong correlation of *MYH9* disease alleles with African ancestry.

In the National Institutes of Health-based study, Kopp and colleagues performed a MALD

scan in 190 African American individuals with biopsy-proven idiopathic or HIV-associated FSGS and in 222 African American controls. They obtained a single prominent linkage peak on chromosome 22 that demonstrated a higher degree of African ancestry than the rest of the genome and occurred close to the 3' end of the *MYH9* gene. Further fine mapping in this gene in a larger group of patients and controls narrowed down the strongest association to single nucleotide polymorphisms (SNPs) defining an at-risk haplotype from exons 14 through 23. This haplotype (E1) conferred an odds ratio of 4.7 (95% CI, 3.1-7.0) for idiopathic FSGS and 5.9 (95% CI, 2.9-12.9) for HIV-associated FSGS, and is carried by 60% of African Americans compared with 4% of European Americans.

In the other study by Kao and colleagues at the Johns Hopkins University, the MALD scan was performed in 1,372 African American patients with ESRD drawn from the Family Investigation in Nephropathy and Diabetes (FIND) and the

Choices for Healthy Outcomes in Caring for ESRD (CHOICE) studies, and from 806 African American controls. Only suggestive evidence for linkage between disease and African ancestry was initially obtained at an overlapping genomic region on chromosome 22, but separate analyses for nondiabetic and diabetic participants with ESRD showed this peak to be driven solely by the nondiabetic participants, a subgroup consisting predominantly of hypertensive kidney disease, FSGS, and HIVAN. This genomic region contained the *MYH9* gene and showed European ancestry estimates that were lower than the genome average in nondiabetic patients with ESRD. The investigators proceeded to genotype 14 SNPs in the *MYH9* gene that defined an at-risk haplotype extending between introns 3 and 23 with highly significant associations to nondiabetic patients with ESRD even after correcting for global ancestry.

MYH9 is the gene encoding nonmuscle myosin IIA heavy chain, a cytoskeletal contractile protein that is constitutively expressed in podocytes and also found in platelets. Mutations in the gene have been associated with syndromes of thrombocytopenia, nephritis, and deafness.^{30,31}

HOW DO THESE STUDIES COMPARE TO PRIOR STUDIES?

Genome-wide association studies for kidney disease phenotypes have yet to yield major successes.³²⁻³⁴ Linkage scans for nondiabetic nephropathy in African American families have yielded several peaks but failed to detect robust linkage to disease.^{35,36} Linkage scans identify the cosegregation of a marker with disease within families and the more widely used nonparametric methods relate a greater degree of allele sharing between relative pairs to similarity in phenotype. Family-based linkage studies have been instrumental in identifying Mendelian forms of FSGS involving podocyte proteins due to highly penetrant mutations.³⁷ However, the vast majority of FSGS is better characterized as a complex disease.

Early successes with admixture mapping have identified genetic loci for prostate cancer, multiple sclerosis, and hypertension.³⁸ Within nephrology, the FIND study has assembled a multiethnic cohort and will exploit the differential

prevalence of diabetic kidney disease between different ethnic groups to identify genetic determinants of diabetic nephropathy using the MALD approach.³⁹

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

These are the first reports of a susceptibility gene for kidney disease in the African American population that appears to explain the excess risk for certain forms of kidney disease, namely FSGS and nondiabetic ESRD. The association to overlapping genomic regions of the gene *MYH9* on chromosome 22 was strong and robust, with similar results reported by 2 different groups of investigators.

The lack of an association for *MYH9* with ESRD due to diabetes in these reports is especially notable, as it suggests disease-specific genetic predispositions and moves us closer to a new understanding of nondiabetic kidney disease, and in particular, of FSGS. Nondiabetic kidney disease in the African American population is considered for the most part a consequence of hypertensive nephrosclerosis. In the clinical setting, hypertensive nephrosclerosis is often a diagnosis of exclusion, histologically characterized by nonspecific findings of segmental or global glomerulosclerosis, leading Freedman and Sedor to suggest that this condition may actually be the manifestation of an underlying primary renal disease in African Americans.⁴⁰ The discovery of the *MYH9* gene supports this hypothesis by invoking a unifying genetic basis for nondiabetic kidney disease in African Americans, where the phenotypic expression may be conditioned on the interplay of additional genes and environmental influences. A recent report of the association between the *MYH9* E1 haplotype and albuminuria in African Americans, but not European Americans, in a cohort enriched for hypertensive families lends further support for this hypothesis.⁴¹ A similar model is offered by *MYH9* gene mutations causing macrothrombocytopenias that are believed to belong to a continuous spectrum of clinically related phenotypes.³¹ Clearly, the structural correlates of *MYH9* and related gene variants, and mechanisms relating gene to disease, need to be elucidated and disease entities such as hypertensive nephrosclero-

sis need to be revisited with detailed histological and molecular characterization.

Are there wider implications for kidney disease in the African continent? Available reports cite “hypertensive nephrosclerosis” as the leading cause of ESRD in Sub-Saharan Africa, followed by “chronic glomerulonephritis,” while HIV-associated disease is of growing significance.^{42,43} How much is attributable to *MYH9*-associated kidney disease? Is the entity exclusively African? How prevalent are the risk alleles or haplotypes? What were the evolutionary pressures that led to selection for these alleles? Given that the region contains a number of genetically distinct populations and that disease risk appears to differ by geographic origin,⁴⁴ far greater genetic complexity is likely.

The findings in these 2 papers are unique as *MYH9* is a major effect gene with a high allelic/haplotypic relative risk. However it is conceivable that there are multiple kidney disease genes in other areas of the genome with a high percentage of African ancestry that underlie differences in disease susceptibility, expression and severity, and possibly, therapeutic response.⁴⁵ The use of innovative study designs and analytic strategies such as MALD would be a major step in understanding the biological basis of race-based disparities in kidney disease.

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