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# Hypertension-Associated Kidney Disease: Perhaps no More

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## ABSTRACT

Despite common wisdom, the role of essential hypertension in the etiopathogenesis of ESRD has been controversial. Two recently published studies demonstrated a strong association of genetic variants in the gene that encodes the molecular motor protein nonmuscle myosin 2a (*MYH9*) with ESRD in African American patients without diabetes. These new data demonstrate that much of the excess risk of ESRD in African American individuals is attributable to an *MYH9* risk haplotype and suggest that hypertension may cause progressive kidney disease only in genetically susceptible individuals or be the result of a primary renal disease.

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Few kidney diseases remain as controversial as hypertensive or arteriolar nephrosclerosis, a syndrome that reportedly progresses to hypertension-associated ESRD.[1–3] Nearly 30% of Americans initiating renal replacement therapy receive this nonspecific moniker each year.[4] Suggesting that essential hypertension does not cause ESRD would seem laughable today, akin to suggesting that *Helicobacter pylori* infection does not underlie modern peptic ulcer disease, yet an alternative story is rapidly unfolding.

Hypertensive nephrosclerosis is a vaguely defined clinical entity, most commonly applied to African Americans with hypertension and advanced chronic kidney disease (CKD) in the absence of other causes for renal failure. Physician bias clearly contributes to ethnic differences in the frequency of diagnosis.[5] In practice, this nonspecific label is applied to African American patients with CKD who do not have diabetes, lack renal biopsies and have secondarily elevated BP with resultant left ventricular hypertrophy.[6] Small studies purport that proteinuria ranging from mild to nephrotic range are seen in this grouping, although a general consensus is that subnephrotic levels of urinary protein excretion are typical of hypertensive nephrosclerosis. Phenotype criteria used in the African American Study of Kidney Disease and Hypertension (AASK) required that daily protein excretion be $<2.5$ g.[7,8]

Although nephrologists agree that elevated systemic BP exacerbates all forms of CKD, speeding progression to ESRD, the epidemiologic evidence supporting mild to moderate essential hypertension as an initiator of kidney damage has always been weak. Recent molecular genetic breakthroughs now demonstrate that genetic variants within a molecular motor protein, nonmuscle myosin IIA, are associated with nondiabetic kidney disease in African Americans,[9,10] suggesting it may often be kidney injury that generates the high BP and not the other way around.[11]

## ESSENTIAL HYPERTENSION: AN UNCOMMON INITIATOR OF PROGRESSIVE RENAL FAILURE?

Cross-sectional studies revealed positive relationships between the severity of kidney dysfunction and degree of BP elevation.[12] Although causation is presumably the basis for this association, severe secondary hypertension is not unexpected in those with marked kidney dysfunction. Relative to European Americans, African American residing in the southeast are at 20-fold greater risk for developing ESRD from hypertensive nephrosclerosis.[13] The increased frequency and severity of high BP in African Americans does not account for the excess rate of hypertensive kidney failure,[14,15] and renal transplantation from normotensive donors largely cures high BP,[16] demonstrating that high BP follows the kidney in humans, as in animal models. In practice, relatively few hypertensive African Americans or European Americans with normal kidney function initially develop progressive nephropathy, with or without antihypertensive therapy.[17] Most im-

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portant, lowering BP to usual or low levels, even with inhibitors of angiotensin II action, does not slow progression of nephropathy in hypertensive African American,[2,18–21] and the renal histologic changes normally associated with high BP, arterial and arteriolar wall thickening, do not correlate with systemic BP.[22,23] Renal biopsies in patients with a clinical diagnosis of hypertensive nephrosclerosis typically reveal segmental or global glomerulosclerosis with marked interstitial fibrosis and other glomerular diseases in the remainder.[22,24]

It has long been proposed that a primary renal disease could explain all of these findings such that observed elevations in BP would be secondary.[24,25] Familial aggregation of hypertensive nephrosclerosis is widely found throughout the United States, with relatives of patients with hypertensive nephrosclerosis frequently having different kidney diseases, including unspecified chronic glomerulonephritis, FSGS, lupus nephritis, and HIV-associated nephropathy (HIVAN).[26]

Why then has the name "hypertensive kidney disease" stuck for all these years? To convince epidemiologists and those with vested interest in the primacy of hypertension that high BP might be a sequela of kidney disease—that hypertensive kidney disease was an inappropriate name for this common condition—it would be necessary to identify major susceptibility genes associated with structural renal changes in African Americans labeled as having hypertensive nephrosclerosis.

## MOLECULAR GENETIC ANALYSES IN NONDIABETIC NEPHROPATHY

As in hypertensive nephrosclerosis, African Americans more often develop nephrotic and non-nephrotic forms of FSGS compared with white individuals.[27,28] Autosomal dominant, steroid-resistant forms of FSGS are caused by $\alpha$-actinin-4 and transient receptor potential cation channel 6 gene polymorphisms, whereas autosomal recessive glomerulosclerosis is caused by podocin (*NPHS2*) and nephrin (*NPHS1*) polymorphisms.[29,30] Renal biopsies in patients with clinically diagnosed hypertensive nephrosclerosis often reveal FSGS, but this entity has been relatively overlooked as a common contributor to hypertensive nephrosclerosis.[22,24] Unusual variants in the podocin and Wilms' tumor (*WT1*) genes make minor contributions to sporadic cases of hypertensive nephrosclerosis and FSGS in African Americans, but these variants are not major causes.[31,32]

Polymorphisms in a candidate gene important in sympathetic nervous system function related to hypertension is associated with hypertensive nephrosclerosis in some African American patients.[33] O'Connor *et al.*[34] evaluated the role of chromogranin A (*CHGA*) in the susceptibility to high BP in kidney disease. *CHGA* gene polymorphisms were associated with hypertensive nephrosclerosis in African Americans from Los Angeles, with validation in patients from the southeastern United States.[33] Thus, *CHGA* clearly contributes to disease in a subset of patients with CKD from hypertensive nephrosclerosis.

Associations with *CHGA*, *WT1*, and *NPHS2* make it seem likely that several genes with relatively small effect are likely involved in the seemingly heterogeneous syndromes termed hypertensive nephrosclerosis and FSGS. In present times, there have been few major "genetic hits" in common complex diseases. Variants of *TCF7L2* gene, for example, demonstrate the strongest association with type 2 diabetes, an effect observed in multiple ethnic groups.[35] A doubling of risk for type 2 diabetes is seen in those homozygous for *TCF7L2* risk alleles.[36] More than 15 other replicated genes are also involved in the susceptibility to type 2 diabetes.[37]

Until now, it seemed that hypertensive nephrosclerosis would likely involve similar numbers of genes. The renal syndrome FSGS ultimately provided the breakthrough for detecting a single major gene in what had often been mislabeled clinically as hypertensive nephrosclerosis but not until the novel analytic technique of mapping by admixture linkage disequilibrium (MALD) was applied.[38] MALD is most useful in the study of inherited diseases that have marked ethnic differences in disease frequency. It uses genetic markers that are spread throughout the genome and have large differences in allele frequency between parental populations.[39] African Americans are an admixed population with a large percentage of African and a lesser proportion of European alleles. Because African Americans develop FSGS and hypertensive nephrosclerosis far more often than white individuals, the expectation would be that regions of the genome that demonstrate an excess frequency of African ancestry in patients with these common kidney diseases would associate with distinct features of a disease.

Kopp *et al.*[9] recently detected an association with genetic markers on chromosome 22q in African Americans with biopsy-proven idiopathic FSGS and HIVAN-associated FSGS. Fine mapping reveals that disease association centers on multiple single nucleotide polymorphisms (SNP) in intron 23 of the nonmuscle myosin IIA heavy chain gene (*MYH9*), a gene expressed in podocytes and implicated in several rare inherited syndromes with glomerular involvement. The most strongly associated single SNP reveal *P* values in the ranges of $10^{-18}$ to $10^{-20}$ with odds ratios (OR) of 4 to 5, whereas a haplotype containing the three most associated SNP had an OR of 5 ($P = 4 \times 10^{-23}$, recessive model). The attributable risk for carriage of this haplotype was 100% in HIVAN-associated FSGS and 72% in sporadic FSGS. Validation was observed in European Americans with idiopathic FSGS, with lower frequency of susceptibility alleles in this ethnic group (4%), and extension studies revealed the African American risk haplotype is significantly associated with nondiabetic forms of ESRD (predominantly classified clinically as ESRD from hypertensive nephrosclerosis) in African Americans (OR 1.7; $P = 0.003$). A previous family-based study failed to detect linkage to chromosome 22,[40] demonstrating the analytic power of MALD.

Additional information on the magnitude of the *MYH9* gene effect is provided by Kao *et al.*[10] working with African American DNA samples from the Family Investigation in Nephropathy and Diabetes (FIND) and Choices for

Healthy Outcomes In Caring for ESRD (CHOICE) studies, also using MALD. Initial admixture analyses of 1372 ESRD patients and 806 control subjects suggested evidence for linkage on chromosome 22. Admixture scans were then performed separately for the 669 patients with nondiabetic ESRD and the 703 with diabetic ESRD. Genome-wide significance was not detected in those with diabetic ESRD, in contrast to a highly significant log of the odds score of 5.70 in a nondiabetic ESRD cohort. The highest single point log of the odds score was 8.56 on chromosome 22 in nondiabetic ESRD cases, the associated region containing the *MYH9* gene. Subsequent analysis of 14 *MYH9* SNP in all patients without diabetes and with ESRD confirm the association, with Bonferroni-corrected *P* values as low as $10^{-14}$ and an OR of 1.90. Estimating the effect of replacing African ancestry at the disease locus with European-derived ancestry would remove approximately 70% of cases of nondiabetic ESRD in the African American population. Significant association was detectable separately among cases with FSGS, hypertensive nephrosclerosis, and all nondiabetic ESRD.

The studies by Kopp *et al.* and Kao *et al.* reveal the powerful contribution of a single gene to multiple related renal syndromes with a substantial effect size for what was previously thought to be a complex disease. The markedly lower frequency of the *MYH9* risk haplotype in European Americans, compared with African Americans, provides a potential reason for the observed ethnic differences in prevalence of FSGS, hypertensive nephrosclerosis, and HIVAN. These results support the concept that *MYH9* is associated with clustering of disparate forms of ESRD in African American families, an unusual observation in European Americans.[1]

## DISPOSING OF THE TERMINOLOGY "HYPERTENSION-ASSOCIATED KIDNEY DISEASE"

Does mere genetic association of the gene encoding the nonmuscle myosin IIA heavy chain with hypertension-associated ESRD exclude a primary role for high BP in disease causation? No, because hypertensive nephrosclerosis is clearly a heterogeneous disorder and hypertension may be one trigger for glomerulosclerosis in genetically susceptible individuals. Hypertensive nephrosclerosis is often misdiagnosed and likely includes cases of both FSGS and non-FSGS glomerular diseases and unrecognized malignant hypertension, renal artery stenosis, or cholesterol emboli syndrome. In addition, not all individuals affected with hypertensive nephrosclerosis will have the associated *MYH9* haplotype; however, the majority of hypertensive African American patients with CKD and low-level proteinuria have segmental or global glomerulosclerosis on renal biopsy. Primary FSGS and HIVAN both are strongly associated with the *MYH9* gene. Interestingly, MYH9 mutations are linked to a number of giant platelet disorders and incompletely penetrant glomerular diseases.[41,42]

Myosin-IIA is a mechanoenzyme that uses the energy of ATP hydrolysis to move actin filaments and has been localized to the podocyte. Neighboring podocytes are interconnected by specialized cell–cell contacts and the slit diaphragm, and proteins that compose this structure actively regulate actin dynamics and maintain normal podocyte structure.[43] Mutations affecting several podocyte proteins lead to rearrangement of the actin cytoskeleton, disruption of the filtration barrier, and subsequent renal disease. It seems likely, although not yet proved, that mutations in the gene encoding nonmuscle myosin cause podocyte injury and FSGS in the absence of hypertension by disrupting actin dynamics. The effect of immunosuppressive or steroid therapies on limiting progression of renal disease in genetically susceptible individuals remains unknown. A concerning observation is that many patients in both of the *MYH9* association studies had ESRD,[9,10] suggesting current therapies were inadequate. The earlier AASK study demonstrated that angiotensin-converting enzyme inhibitors slowed but did not prevent disease progression in patients with a clinical diagnosis of hypertensive nephrosclerosis, albeit without added benefit from aggressive BP lowering.[20] Hopefully, studies of the mechanisms by which *MYH9* gene variants cause kidney disease will result in new diagnostic tests to allow presymptomatic detection of high-risk individuals and suggest novel pathways involved in renal failure and will allow for new strategies to preserve renal function.

Important lessons from this success story include the value of a tissue diagnosis for characterizing poorly described syndromes such as hypertensive nephrosclerosis and the importance of focusing multidisciplinary research teams with expertise in clinical nephrology, molecular and statistical genetics, and cell biology on complex clinical problems. It seems time to bury the outdated term "hypertension-associated kidney disease." Perhaps "*MYH9*-associated nephropathy" or "*CHGA*-associated nephropathy" will better serve patients in this new era of personalized medicine. Hypertensive nephrosclerosis . . . may you rest in peace.

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## DISCLOSURES

None.

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