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Essential hypertension and risk of nephropathy: a reappraisal

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Abstract

This manuscript reviews the controversial relationship between hypertension and initiation of kidney disease. We focus on ethnic differences in renal histopathology and associated gene variants comprising the spectrum of *MYH9*-nephropathy.

Purpose of review—Treating mild to moderate essential hypertension in non-diabetic African Americans fails to halt nephropathy progression; while hypertension control slows nephropathy progression in European Americans. The pathogenesis of these disparate renal syndromes is reviewed.

Recent findings—The non-muscle myosin heavy chain 9 gene (*MYH9*) is associated with a spectrum of kidney diseases in African Americans, including idiopathic focal global glomerulosclerosis historically attributed to hypertension, idiopathic focal segmental glomerulosclerosis, and the collapsing variant of focal segmental glomerulosclerosis (HIV-associated nephropathy). Risk variants in *MYH9* likely contribute to the failure of hypertension control to slow progressive kidney disease in non-diabetic African Americans.

Summary—Early and intensive hypertension control fails to halt progression of “hypertensive nephropathy” in African Americans. Genetic analyses in patients with essential hypertension and nephropathy attributed to hypertension, FSGS and HIVAN reveal that *MYH9* gene polymorphisms are associated with a spectrum of kidney diseases in this ethnic group. Mild to moderate hypertension may cause nephropathy in European Americans with intra-renal vascular disease improved by the treatment of hypertension, hyperlipidemia and smoking cessation.

Keywords

African Americans; *CHGA*; focal segmental glomerulosclerosis; genetics; hypertensive nephrosclerosis; *MYH9*

Introduction

The causes of end-stage renal disease (ESRD) in the USRDS database are provided by thousands of nephrologists without standardized diagnostic criteria and frequently without kidney biopsies. These diagnoses may not be accurate and physician bias plays a major role in disease classification^{1–5} When nephrologists were provided with identical clinical histories in non-diabetic patients having low level proteinuria and hypertension, they were twice as likely to diagnose hypertensive kidney disease in AA and more likely to diagnose chronic glomerulonephritis in EA⁶. Nonetheless, nephropathy classified as secondary to hypertension is consistently reported as the second most common cause of ESRD in the U.S.⁷. Nearly one-

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third of AA initiating dialysis in the U.S. are labeled with hypertension-associated ESRD, in contrast to 25% of European Americans⁷.

Many attribute the excess frequency of hypertensive nephropathy in AA to the higher prevalence and greater severity of high blood pressure, as well as lower socioeconomic status and poorer access to medical care. However, McClellan et al. reported that ethnic differences in the relative risk of hypertensive renal failure persisted after adjustment for age, sex, and differences in prevalence and severity of hypertension between races⁸. In addition, Rostand et al. reported that hypertensive AA had twice the incidence of declining renal function compared to EA, despite similar initial serum creatinine concentration, initial and treated blood pressures, number of missed office visits and antihypertensive medications prescribed⁹. The Multiple Risk Factor Intervention Trial (MRFIT) also detected a significant decline in kidney function in hypertensive AA compared with non-AA, despite equivalent hypertension control in both ethnic groups¹⁰. Pharmacologic treatment of mild-moderate hypertension in AA has little impact on the incidence of chronic renal failure, whereas it significantly reduces the progression of CKD in EA, along with treatment of hyperlipidemia and smoking cessation^{10–12}.

If mild to moderate hypertension commonly caused kidney failure in AA, early and successful blood pressure control would be expected to reduce the incidence of renal functional decline¹³. However, the Hypertension Detection and Follow-up Program (HDFP), MRFIT, and African American Study of Kidney Disease and Hypertension (AASK) trials uniformly revealed that strict blood pressure control in hypertensive African Americans led to similar declines in renal function compared to standard blood pressure control, even using angiotensin converting enzyme inhibitors^{10;14;15}.

When histopathology was available, AA clinically labeled with “hypertensive nephrosclerosis” typically had focal global and/or focal segmental glomerulosclerosis^{16;17}. An important finding from AASK study was that individuals who underwent kidney biopsy had fairly uniform histology with focal global glomerulosclerosis, interstitial fibrosis and renal microvascular changes, although only 39 patients were evaluated. The vascular changes historically ascribed to hypertension (intimal hyperplasia, luminal narrowing and thickening of the media in small intra-renal blood vessels) did not correlate with systemic blood pressure, suggesting that high blood pressure was not causative. These findings raised the possibility that a primary kidney disease was present and caused secondarily elevated blood pressure¹⁷.

Marcantoni et al. compared the presence of renal histologic changes in EA and AA given the clinical diagnosis “hypertensive nephrosclerosis”¹⁸. Marked ethnic variation was observed, African Americans more often had solidified glomerulosclerosis and EA had obsolescent and collagen-rich glomerulosclerosis. African Americans with non-diabetic nephropathy were generally younger than EA, had similar mean arterial blood pressures, and more prominent arteriolosclerotic changes. The presence of ethnic differences in renal histology, coupled with the relentless renal functional decline in AA with treated hypertension, underscore that the primary lesion in AA with “hypertensive” nephropathy resides in the kidney. In contrast, treating small vessel disease in hypertensive EA by blood pressure lowering and reducing other cardiovascular disease risk factors suggests that hypertension truly initiates kidney disease in these patients.

It is also interesting that AA with hypertension and CKD more often progress to dialysis, whereas EA are more likely to die from cardiovascular causes. This pattern suggests the presence of disparate disease processes between ethnic groups, with renal-limited diseases in AA accounting for less severe systemic atherosclerosis with improved survival¹⁹.

Genetic determinants of non-diabetic kidney disease

The major breakthrough in our understanding of common complex kidney disease came with identification of the association between the non-muscle myosin heavy chain 9 gene (*MYH9*) and idiopathic and secondary forms of FSGS. Marked familial aggregation of kidney disease is observed in AA, often with different causes of kidney disease in family members²⁰. Familial aggregation occurs independently from socioeconomic factors^{21;22} suggesting the presence of a generalized renal failure susceptibility gene. A major gene was recently discovered using Mapping by Admixture Linkage Disequilibrium, a technique valuable in admixed populations displaying ethnic differences in disease frequency. African Americans are an admixed population consisting of approximately 80% African and 20% European genetic make-up. African Americans have a four fold or greater excess risk of all-cause ESRD compared to EA^{23–25} and have particularly high rates of HIVAN and idiopathic FSGS^{26–29}.

Kopp et al. initially identified excess African ancestry on chromosome 22p in AA with idiopathic FSGS and HIV-associated collapsing FSGS, compared to AA³⁰. Fine mapping under the admixture peak identified *MYH9* as the associated gene. *MYH9* was associated with clinically diagnosed “hypertensive ESRD” in AA as well^{30;31}. The Family Investigation in Nephropathy and Diabetes (FIND) Study rapidly replicated association in several non-diabetic forms of ESRD in AA, including idiopathic FSGS, HIVAN and clinically diagnosed “hypertensive-ESRD”³². FIND reported that the population-attributable risk from *MYH9* in AA with non-diabetic ESRD was 70% (70% of non-diabetic cases of ESRD in AA would disappear if *MYH9* risk variants were replaced with the neutral/protective variants more often found in European-derived populations). These studies demonstrated that ethnic differences in susceptibility to non-diabetic ESRD were largely due to heredity, not socio-economic factors or ethnic differences in access to care. Risk variants in *MYH9* are present in 60% of all AA, in contrast to 4% of EA. Ethnic disparities in gene frequency account for much of the ethnic variation in risk for non-diabetic ESRD. The importance of *MYH9* in the disease historically labeled “hypertensive ESRD” was extended in 696 cases diagnosed by their nephrologists, compared with 948 non-nephropathy controls recruited at Wake Forest³³. Strong evidence of association was confirmed, with single nucleotide polymorphism (SNP) odds ratios (OR) as high as 3.4. Thus, the spectrum of *MYH9*-associated nephropathies in AA encompasses idiopathic FSGS, HIVAN, and those with the clinical diagnosis “hypertensive ESRD”. *MYH9* is an overarching renal failure susceptibility gene, acting independently from high blood pressure, hyperglycemia, and HIV infection. *MYH9* was recently shown to underlie approximately 16% of type 2 diabetes-associated ESRD in AA, although it remains unclear whether the disease was FSGS with coincident diabetes or classic diabetic nephropathy.³⁴

Does hypertension “trigger” *MYH9*-associated kidney disease?

Confirmation that *MYH9* was associated with ESRD in multiple AA cohorts raised the question of whether hypertension might cause ESRD in individuals inheriting two *MYH9* risk variants. It was necessary to evaluate large numbers of AA and EA with essential hypertension and measures of proteinuria and kidney function to determine whether *MYH9* was associated with elevated blood pressure in the absence of kidney disease. National Heart Lung and Blood Institute-sponsored Hypertension Genetics (HyperGEN) Study samples were analyzed³⁵. HyperGEN included nearly 1,500 hypertensive AA and 1,500 hypertensive EA with preserved kidney function and measures of albuminuria³⁶. The most striking finding from HyperGEN was that *MYH9* risk allele frequencies were no different in hypertension-enriched cohorts compared to ethnically-matched general populations³⁵. Moreover, *MYH9* was weakly associated with albuminuria in hypertensive AA, but not in hypertensive EA, an effect likely related to inclusion of small numbers of individuals with pre-existing FSGS, as mild-moderate CKD was not an exclusion criterion

To convince those skeptical that high blood pressure does not frequently cause kidney disease in African Americans, it was important to test for *MYH9* gene associations in cases fitting rigorous clinical criteria for hypertensive nephropathy. AASK participants were ideal, since they were uniformly hypertensive, lacked diabetes and had a maximum of 2.5 grams of urinary protein excretion per day. Four *MYH9* single nucleotide polymorphisms (SNPs) have been evaluated in 497 AASK participants. SNP rs4821481, located in the E1 haplotype that is strongly associated with FSGS, HIVAN and “hypertensive ESRD” was strongly associated with kidney disease in AASK participants (OR 1.63; $p=6.5\times 10^{-5}$, recessive). Increasing strength of association was detected in AASK participants with progressive nephropathy and serum creatinine concentrations exceeding 3 mg/dl (OR 2.33; $p=2.4\times 10^{-6}$, recessive)³⁷. Among the 161 AASK subjects with serum creatinine concentrations ≥ 3 mg/dl, *MYH9* SNPs rs11912763 (OR 2.69; $p=0.008$, recessive) and rs1005570 (OR 1.57; $p=0.027$, recessive) were also strongly associated.

The spectrum of *MYH9*-associated kidney diseases in AA now extends from clinically diagnosed hypertensive nephropathy with focal global glomerulosclerosis and interstitial fibrosis on biopsy in AASK participants to ESRD historically attributed to hypertension. Moreover, *MYH9* exhibits the strongest disease association yet detected for common complex human diseases, as seen in idiopathic FSGS and HIVAN. The magnitude of association reveals the presence of a Mendelian-like effect in non-diabetic kidney disease. *MYH9* is also strongly associated with idiopathic FSGS in EA and development of CKD in Europeans^{30;38}. However, the frequency of kidney disease related to *MYH9* in European-derived populations is far lower than in AA due to the reduced frequency of risk alleles. Finally, chromogranin A gene (*CHGA*) polymorphisms are also associated with hypertensive ESRD in AA.^{39;40}

Myosin and *MYH9*

The *MYH9* gene encodes non-muscle myosin class II isoform IIA⁴¹. Myosins constitute a superfamily of proteins interacting with actin and grouped into 15 classes⁴². Myosin class II is subdivided into smooth- and non-smooth muscle myosin II. These myosins are structurally similar and composed of two heavy and two light chains that polymerize and interact with actin. Non-muscle myosin heavy chains (NMMHC) exist in three isoforms (NMMHC-A, NMMHC-B, NMMHC-C), each encoded by different genes (*MYH9*, *MYH10* and *MYH14*, respectively, on chromosomes 22q12.3, 17p13.3, and 19p13.3)⁴³, subdividing non-smooth muscle myosin II into 3 isoforms: IIA, IIB, and IIC⁴².

Non-smooth muscle myosin II isoforms are variably expressed in different tissues. Platelets express only NMMHC-A (II-A)⁴⁴, while fetal and adult human kidneys express isoforms IIA and IIB^{43;45}. Isoform IIA is expressed mainly in glomeruli of mature kidneys (podocytes and mesangial cells), arteriolar and peritubular capillaries^{43;45}. Within podocytes, *MYH9* protein localizes mainly in the foot processes as a continuous narrow layer underneath the plasma membrane⁴⁵.

Myosin IIA is involved in cellular contractility, migration, phagocytosis, actin stress fiber organization, maintenance of cell shape and polarity, cell-cell contact and focal adhesion, and intracellular organelle trafficking^{46;47}. Alterations in myosin IIA protein are clearly relevant to human disease. Heterozygous mutations in *MYH9* cause the *MYH9*-related disease spectrum (*MYH9*-RD) including May-Hegglin Anomaly, Sebastian Syndrome, Fechtner Syndrome, and Epstein Syndrome (Table 1)⁴⁸. Patients with *MYH9*-RD universally exhibit macrothrombocytopenia, while other phenotypic features (leukocyte inclusion bodies, deafness, cataracts, and nephritis) are variably present. The presence of renal manifestations denotes Fechtner Syndrome (with leukocyte inclusions, sensorineural deafness and cataracts) or Epstein syndrome (absence of leukocyte inclusions)⁴⁸. Renal disease in these related

syndromes manifests as glomerulopathy with hematuria, proteinuria, and progressive renal failure with ESRD in the fifth decade, although it has been reported in childhood⁴⁹. Histologic data are scanty and include mesangial matrix expansion, mesangial cell proliferation, podocyte foot process effacement, variable degrees of capillary wall basement membrane thickening and basket-weave splitting, leading to global glomerulosclerosis in a case report containing repeat kidney biopsies⁴⁹. Wide phenotypic variability is seen, with single mutations in a family or unrelated individuals causing a spectrum of renal manifestations⁴⁵. This fostered the concept that *MYH9* syndromes are not distinct entities, but a single disorder with variable manifestations⁴⁸.

***MYH9* and glomerulosclerosis - potential pathogenetic mechanisms**

A healthy podocyte cytoskeleton is required to maintain cellular architecture and fulfill the filtration barrier function^{50;51}. Mutations in genes encoding podocyte proteins interacting with the actin cytoskeleton, including alpha-actinin 4⁵², CD2-associated protein⁵³ and synaptopodin⁵⁴ are associated with FSGS. Myosin IIA is a component protein of the podocyte cytoskeleton⁵⁵. Dysregulated podocyte myosin function and consequent actin cytoskeleton abnormalities might lead to inability to withstand hydraulic pressure and maintain capillary integrity, foot process retraction, quantitative diminution of glomerular basement membrane collagen IV synthesis^{45;56}, and resultant glomerulosclerosis.

Epithelial tissues depend heavily on cell-cell adhesions, requiring correct localization of junctional components such as E-cadherin, zonula occludens and β -catenin for function. Myosin II is critical for concentrating E-cadherin at these sites⁵⁷ and loss of E-cadherin may be involved in epithelial-mesenchymal transition (EMT)⁵⁸. Glomerular EMT has been proposed as important in development of glomerular disease^{59,60} and provide a possible link between *MYH9* and glomerulosclerosis.

Platelet influx in the glomerulus has also been implicated in glomerulosclerosis and glomerular obsolescence in animal models using renal ablation^{61–63}. As *MYH9* polymorphisms are associated with syndromes characterized by abnormal platelet size and function⁶⁴, glomerular platelet accumulation with resultant ischemia and release of TGF- β and PDGF could potentiate *MYH9*-associated nephropathy^{65;66}.

Gene-gene and gene-environment interactions in *MYH9*-nephropathy

Although *MYH9* demonstrates strong association with human disease, inheriting two *MYH9* risk variants appears insufficient to initiate nephropathy. Approximately 4% of AA inheriting two *MYH9* risk variants developed idiopathic FSGS, while approximately 20% with HIV infection and two risk variants developed collapsing FSGS or HIVAN (Jeffrey Kopp, personal communication). This demonstrates that HIV1 viral infection, an environmental factor, yields a fivefold increase in risk. Importantly, approximately 80% of genetically susceptible AA with HIV infection will not develop HIVAN and 96% of HIV-negative AA risk homozygotes will not develop FSGS. In the absence of HIV infection, C1q nephropathy can also manifest a collapsing phenotype in the presence of *MYH9* risk variant homozygosity.⁶⁷ This strongly implicates a “second hit” whereby individuals with genetic susceptibility to kidney disease require an additional factor(s) to initiate nephropathy. We believe that *MYH9* gene-gene and *MYH9* gene-environment interactions exist (Figure 1). For example, it will be important to evaluate *MYH9* gene products for interaction with podocin and other proteins comprising the podocyte cytoskeleton and slit diaphragm.

Environmental factors such as HIV infection can clearly trigger *MYH9*-associated nephropathy. It will be important to evaluate the roles of nephropathic viruses including polyoma viruses and parvovirus B19. It is also possible that lymphotropic viruses related to

HIV1 initiate kidney disease in susceptible AA and HTLV-1, HTLV-2, CMV, and Human Herpes 6 are prime candidates, although HIV1 directly infects podocytes.

These possibilities provide new hope for preventing kidney disease in those with genetic predisposition from *MYH9*. If viral infections initiate glomerulosclerosis, vaccines preventing infection could prevent renal insufficiency. As aggressive blood pressure control and use of ACE-inhibitors fail to halt progression of *MYH9*-associated kidney diseases, novel strategies to maintain podocyte cytoskeletal architecture have the potential to prevent glomerulosclerosis in AA with the disorder that has historically been labeled hypertensive nephrosclerosis.

CONCLUSIONS

Longstanding physician bias and misclassification have confused the classification of chronic forms of nephropathy. High blood pressure is not a common inciting factor for hypertensive nephrosclerosis in AA. In contrast, small vessel disease related to high blood pressure and other cardiovascular risk factors is often present in older EA given this diagnosis. Nonetheless, it remains critical to aggressively treat high blood pressure in those with (and at risk for) kidney disease. Hypertension accelerates nephropathy progression in all proteinuric kidney diseases⁶⁸ and contributes to heart failure, myocardial infarction and stroke^{69–71}. Seventy percent of AA with non-diabetic kidney disease fall into the spectrum of *MYH9*-associated nephropathy, ranging from focal global glomerulosclerosis in AASK participants, to sporadic FSGS, to collapsing glomerulopathy related to HIV infection. It is unclear why these different histologic disease patterns develop, although it is tempting to speculate that different modifier genes or environmental factors interacting with *MYH9* dictate renal lesions. These recent genetic studies made major contributions toward untangling the complex relationship between high blood pressure and initiation of kidney disease. *MYH9*-related podocyte cytoskeleton dysregulation with progressive nephron loss likely cause secondary hypertension in African Americans labeled as having hypertensive nephropathy.

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Abbreviations

AA	African American(s)
EA	European American(s)

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Figure 1.

Classification and postulated mechanisms for the *MYH9*-associated nephropathies

Table 1

MYH9 - disease associations

Idiopathic FSGS
Focal global glomerulosclerosis (previously labeled "hypertensive renal disease")
Collapsing FSGS (HIVAN & C1q nephropathy)
Fechtner syndrome; Sebastian syndrome
Autosomal dominant macrothrombocytopenia (May-Hegglin related disorders)
Schizophrenia (subgroup with preserved attention and executive function)
Congenital cleft lip and/or cleft palate