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The Spectrum of *MYH9*-Associated Nephropathy

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Abstract

Causes of the excess incidence rates of chronic kidney disease in the African American population have long been under study. Recently, polymorphisms in the nonmuscle myosin heavy chain 9 gene (*MYH9*) have been associated with nondiabetic kidney diseases in African- and European-derived populations. Risk variants in *MYH9* contribute to approximately 70% of nondiabetic forms of ESRD in African Americans and 40 to 45% of all ESRD in this ethnic group, with lesser effects in European Americans. It is clear that *MYH9* polymorphisms have a significant impact on the incidence rates of kidney disease in African Americans. This article describes the current spectrum of biopsy-proven *MYH9*-associated kidney diseases, along with potential effects of *MYH9* on ethnic differences in clinical outcome. *MYH9* risk variants exhibit the most impressive association with any common complex kidney disease yet identified.

The search for genes underlying susceptibility to nondiabetic, potentially hypertension-associated forms of ESRD arose in part from the controversy over whether mild to moderate essential hypertension commonly initiated chronic kidney disease (CKD) ([1,2]). The epidemiology of ESRD in the US Renal Data System database may not be fully accurate ([3]). Hypertension-associated ESRD reportedly accounts for >34% of incident African American dialysis cases and nearly 25% of European American cases ([4]). African Americans clearly develop nondiabetic forms of ESRD more often than do European Americans ([4]); however, relatively few patients with mild to moderate essential hypertension ultimately develop CKD ([5,6]), and the disorder labeled hypertensive ESRD aggregates in select African American families. These factors suggested an inherited basis for hypertensive nephrosclerosis (HN).

Complicating the issue of whether high BP initiates nephropathy, it was reported that physician bias led to a diagnosis of HN far more often in African Americans ([7]), individuals with a diagnosis of HN were typically seen by nephrologists late in their course when it was difficult to identify initiators of kidney disease ([8]), and renal biopsy studies in African American patients did not support that the vascular change “arteriolar nephrosclerosis” correlated with systemic BP ([9,10]). An important clue that the disease process labeled HN

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differs between European Americans and African Americans arose from kidney biopsy studies. Those studies revealed different renal lesions in African American and European Americans who were given the same clinical diagnosis "HN" ([11]). African American patients typically had focal global glomerulosclerosis (FGGS) with marked interstitial fibrosis, whereas European American patients demonstrated intimal medial thickening of small intrarenal arterioles with resultant reduced renal perfusion and ischemic glomerular collapse. European American patients with HN often demonstrate stabilization of kidney function and albuminuria with successful treatment of high BP, hyperlipidemia, and smoking cessation ([12–15]). Treatment of these cardiovascular risk factors is expected to improve renal microvascular disease, the process seen in European Americans with HN. In contrast, the primary site of renal injury in African American patients labeled with HN does not seem to be the microvasculature. The African American Study of Kidney Disease and Hypertension (AASK) demonstrated that strict BP control, including the use of angiotensin-converting enzyme inhibitors, failed to halt progression of the kidney disease that had been attributed to hypertension ([16]).

These phenomena, coupled with familial clustering of HN in African Americans, led to a search for nondiabetic nephropathy susceptibility genes. Other potential explanations for the higher frequency of severe kidney disease in African Americans include lower socioeconomic status, lack of access to adequate health care, and more severe hypertension ([17]). The recently detected major contribution of risk variants in the nonmuscle myosin heavy chain 9 gene (*MYH9*) to ESRD susceptibility in African Americans clearly demonstrates that inherited factors make major contributions to the aforementioned ethnic disparities ([18–20]).

MYH9 and Susceptibility to CKD

Familial aggregation of the common forms of CKD, including diabetic nephropathy and purported HN, had been recognized for 20 years ([21–27]). Thirty to 40% of individuals with type 1 and type 2 diabetes are at risk for the development of nephropathy. As commonly seen in HN, diabetic nephropathy clusters in select families. This observation shifted our understanding of CKD risk factors. Instead of the prevailing concept that patients with the most severely elevated BP and blood sugar levels were more likely to develop nephropathy, it become apparent that CKD susceptibility from systemic disorders could have an inherited basis.

Familial aggregation of ESRD is strongest in the African American population and has been observed with additional forms of CKD, including FSGS, HIV-associated nephropathy (HIVAN), and systemic lupus erythematosus. ([28,29]) The observations that familial clustering was independent of socioeconomic factors ([28,30]) and that multiple causes of CKD often clustered in African American families suggested that an overarching "renal failure susceptibility gene" was present ([31]).

Results of linkage analyses and candidate gene association studies in nondiabetic ESRD have been reported in African Americans; however, it was not until the application of admixture mapping or mapping by admixture linkage disequilibrium that *MYH9* was

identified. Mapping by admixture linkage disequilibrium is a useful method to detect gene variants that contribute to diseases in admixed populations in which the ancestral populations have markedly different disease frequencies ([32]). African Americans are known to have a fourfold increase in risk for all cause ESRD, relative to European Americans ([4]). Diseases such as HIVAN occur up to 70 times more often in the African American population. Assuming that risk variants in kidney failure genes were derived from Africa, it was possible to compare the frequencies of approximately 1500 ancestry-informative markers spaced evenly across the genome in African Americans with nondiabetic renal diseases (FSGS and HIVAN) with those in African Americans with normal kidney function ([18],[19]). Admixture mapping analyses demonstrated a 10% excess frequency of African ancestry on chromosome 22 with a major peak overlying the *MYH9* gene. Follow-up genotyping identified a four–single-nucleotide polymorphism (SNP) haplotype (G/C/C/T; rs4821480, rs2032487, rs4821481, and rs3752462) in *MYH9* that was strongly associated with FSGS, HIVAN, and the kidney disease historically attributed to HN in African Americans (Figure 1) ([18]). The risk haplotype that was referred to in the article by Kopp *et al.* ([18]) as E-1 (for Extended-1) has a frequency of approximately 60% in African Americans and 4% in European Americans with odds ratios (ORs) for association with FSGS of 5.0 and 7.7, respectively. These effect sizes are extremely large for common, complex human diseases.

Subsequent analyses demonstrated that the population-attributable risk from possessing *MYH9* risk alleles approximates 70% in nondiabetic ESRD in African Americans; this effect was computed using the E-1 haplotype as the surrogate risk variant (95% confidence interval 55 to 81%) ([19]). Stated another way, replacement of *MYH9* risk variants in the African American population with protective or neutral variants (as are often seen in the European American population) would reduce the rates of nondiabetic ESRD by a staggering 70%. Fine mapping studies are under way in an attempt to identify causative *MYH9* SNPs. Additional studies will then be necessary to understand the population risk incurred by these *MYH9* polymorphisms. It is also clear that additional factors beyond genotype must be important in the initiation of the *MYH9*-associated spectrum of kidney disease ([20]).

It is generally accepted that common complex diseases are not the result of mutation in a single gene but rather the cumulative effect of multiple genetic and environmental factors. For example, although nearly 40 type 2 diabetes susceptibility genes have been identified, in aggregate, they contribute to <10% of the total risk for developing diabetes ([33]). The strongest and most replicated diabetes genes, such as *TCF7L2*, contribute approximately a 40% increase in risk for each risk variant that is inherited ([34]). In contrast, *MYH9* contributes a far stronger effect on the risk for kidney disease in African American and European-derived populations.

MYH9 encodes the nonmuscle myosin heavy chain 9, which, with other subunits, forms myosin II ([35]). Myosin II is a motor protein that binds actin and is involved in cellular motility. *MYH9* is expressed in the podocyte, as well as in mesangial cells and arteriolar and peritubular capillaries ([36]). We postulate that a mutation in the *MYH9* gene product could produce podocyte injury with FSGS, although other mechanisms, including interactions

between glomerular cells and abnormal platelets, remain possible and warrant further study. *MYH9* mutations had been implicated in a number of autosomal dominant syndromes: May-Hegglin, Sebastian, Fechtner, and Epstein ([37,38]). These syndromes are platelet disorders that are characterized by thrombocytopenia and leukocyte inclusions, with Fechtner and Epstein syndromes resulting in nephritis to varying degrees. The mutations identified in these cases are nonsense or missense mutations that result in significant structural mutations in *MYH9* and platelet abnormalities. Despite the structural mutations, few of these patients develop renal failure. It is unclear why structural defects would not necessarily result in renal failure in the autosomal dominant syndromes, whereas the variants that are associated with ESRD in African Americans are intronic and confer significant risk. Functional studies on these variants will be an important future step in understanding the role of *MYH9* in ESRD.

"Second Hits" in *MYH9*-Associated Nephropathy

Initial reports revealed that approximately 35% of the general African American and 1% of the European American population are homozygous for the *MYH9* E-1 risk haplotype ([18 – 20]); however, approximately 4% of African Americans who are homozygous for the *MYH9* E-1 risk haplotype will develop idiopathic FSGS, whereas 20% of HIV-infected E-1 homozygous African Americans develops HIVAN (Jeffrey Kopp, personal communication, November 2009). Because African Americans with two *MYH9* risk variants do not uniformly develop nephropathy, co-factors for initiation of renal disease must exist (Figure 2). It is clear that viral infections can contribute to risk, on the basis of the fivefold excess frequency of nephropathy in HIV-infected *MYH9* risk homozygotes. Nonetheless, four of five HIV-infected African Americans who are homozygous for *MYH9* risk variants do not develop nephropathy. This led us to hypothesize that "second hits," or additional factors, are required to initiate kidney disease.

On the basis of the role of HIV infection in *MYH9*-associated HIVAN ([39]), we postulate that gene– environment interactions could produce renal disease in *MYH9* risk homozygotes. Several non-HIV viral infections are associated with CKD, including BK virus and Parvovirus B19 ([40,41]). We postulate that these or other viruses that can infect renal cells or lymphocytes contribute to development of *MYH9*-associated nephropathy in the manner of HIV1 viral infection.

In addition, it remains possible that gene– gene interactions may be factors. Polymorphisms in podocin, ex actinin-4, and *TRPC6* have been shown to contribute to glomerulosclerosis ([42_ 44]). It is conceivable that heterozygous mutations in these or other genes coupled with *MYH9* risk homozygosity may ultimately produce susceptibility to FSGS. For example, disruption of *MYH9* alone may not be sufficient to result in significant podocyte structural malfunction; however, mutation of other cytoskeletal components, such as ex actinin-4, in addition to *MYH9* may substantially damage the structure of the podocyte and impair its function as a filtration barrier. Studies to investigate these possibilities are actively under way.

Essential Hypertension and Initiation of *MYH9*-Associated Nephropathy

As discussed in the beginning of this article, although hypertension is often listed as a cause of ESRD in African Americans, familial clustering of other forms of CKD, including diabetic nephropathy, chronic glomerulonephritis, lupus nephritis, and HIVAN in families with index cases who have "hypertensive ESRD," suggested the presence of an overarching kidney failure susceptibility gene ([1,24]). An association analysis of 696 African Americans who reportedly had hypertensive ESRD revealed the important contribution made by *MYH9* polymorphisms, with SNP association OR as high as 3.4 ([20]). In addition, multiple regions in *MYH9* seem to produce independent susceptibility, including the major E-1 haplotype (OR 2.4), the recently identified L-1 haplotype (A/G/C/T; rs7078, rs12107, rs735853, and rs5756129; OR 1.9), and one additional SNP, rs5756152 (OR 2.3). This suggests that the disease labeled HN resides in the FSGS family ([2]).

An association analysis in the NHLBI-Hypertension Genetics Study (HyperGEN) demonstrated weak association between albuminuria and *MYH9* polymorphisms ([45]). Of greater importance, the frequency of the E-1 risk haplotype was not different in the HyperGEN African American population with hypertension when contrasted to the control populations in previous reports ([18 –20]). This suggests that *MYH9* does not play a major role in susceptibility to essential hypertension.

We recently reported that putative HN in AASK participants was strongly *MYH9* associated ([46]). *MYH9* E-1 haplotype SNP rs4821481 had an OR of 1.99 ($P = 7 \times 10^{-6}$, recessive) in those with serum creatinine concentrations ≥2 mg/dl, increasing to OR 2.7 with serum creatinine concentrations >3 mg/dl. Thus, FGGS in AASK falls within the spectrum of *MYH9*-associated disorders. Patients with FGGS in AASK were similar to those with "hypertensive ESRD" in the Wake Forest cohort ([20]), considering the risk imparted by *MYH9*.

Collapsing FSGS: The Most Aggressive Lesion in the Spectrum

FSGS is a disorder of podocyte depletion ([47]). In contrast, HIVAN is manifested by abnormal extensive proliferation of podocytes, cells that are normally terminally differentiated. Recent results showed that HIV can directly infect the podocyte, and a series of interrelated pathways leads to loss of the differentiated phenotype with extensive proliferation and resultant glomerular collapse ([39]). HIV1-specific gene products may be involved in this process and interact with *MYH9*. It also remains possible that other environmental and genetic co-factors are second hits necessary for the development of podocyte proliferation. It recently became clear that mesangial immune complex deposition can also trigger the collapsing variant of *MYH9* nephropathy. HIV-negative African Americans with mesangial C1q-containing immune complexes have developed collapsing glomerulopathy in the presence of *MYH9* risk variants ([48]). This broadens the spectrum of collapsing FSGS to include immune complex–mediated diseases and effects of viral infection. The effects of *MYH9* risk variants on development of the idiopathic variant of collapsing FSGS, the most common cause, is unknown; however, there is no reason to

suspect that *MYH9* does not underlie this form of collapsing FSGS. This is an important renal lesion that warrants additional analysis.

The Evolving Spectrum of *MYH9*-Associated Nephropathy

The association of risk variants in *MYH9* with nondiabetic forms of nephropathy in African Americans and European-derived populations demonstrates among the strongest association with any common complex human kidney disease. In addition, although the OR for *MYH9* association with type 2 diabetic nephropathy in African Americans is 1.4 (far lower than for FSGS, HIVAN, and FGGS), approximately 16% of African Americans who receive a clinical diagnosis of type 2 diabetes–associated ESRD have disorders in the *MYH9* spectrum ([49]). We believe that it is most likely that these patients actually have FSGS with coincident diabetes, although kidney biopsy studies remain to be performed to demonstrate whether the classic histologic changes that are seen in diabetic nephropathy are present. Nonetheless, *MYH9* contributes to 40 to 45% of all ESRD in the African American population, as well as FSGS and CKD in Europeans and European Americans.

The emerging spectrum of *MYH9* nephropathy clearly links FGGS (the disease historically attributed to hypertension), idiopathic FSGS, and collapsing variants of FSGS secondary to HIV infection and C1q immune complex deposition (Figure 3). This disease spectrum explains the presence of multiple causes of CKD in single African American families, a phenomenon rarely observed in non–African American families. This finding has important implications, including an inherited mechanism of disease in the African American population, although the contribution of environmental risk factors to initiation of kidney scarring should not be downplayed.

The implications and novel questions raised by this observation extend beyond the epidemiology of CKD (Table 1). The unexplained poorer allograft survival of kidneys that are donated by African Americans may be attributable, in part, to *MYH9* mutations. Deceased-donor kidneys from African Americans survive less well than kidneys that are donated by European Americans, whether transplanted into African American or European American recipients ([50,51]). It is possible that the combined effects of cold ischemia time, nephrotoxic calcineurin inhibitors, and donor–recipient genotype interactions may interact with *MYH9* to explain this phenomenon.

The rapidly expanding spectrum of *MYH9*-associated kidney diseases has been a major breakthrough in our understanding of the epidemiology of ESRD, particularly in the African American population. The effects of various second hits may dictate the type of *MYH9*-associated renal lesion. For example, HIV infection most commonly yields collapsing glomerulopathy, whereas other co-factors might produce FGGS or classic FSGS. The role of these co-factors and resultant renal histologic patterns remain important to determine. It is abundantly clear that mild to moderate forms of essential hypertension are insufficient to initiate kidney disease among *MYH9* risk homozygotes. The majority of African Americans who have low-level proteinuria and are labeled as having HN and hypertension-associated ESRD have an incorrect diagnosis. We remain optimistic that identification and treatment of environmental second hits, as well as drug therapies directed at maintaining the normal

podocyte cytoskeletal architecture, offer hope for the prevention of CKD in the African American population. *MYH9* encodes a motor protein involved in the movement of actin filaments in the podocyte and is also expressed in other renal cells. We believe that alterations in podocyte architecture lead to the spectrum of *MYH9*-associated nephropathies, because FSGS is commonly associated with other gene polymorphisms that interrupt the podocyte cytoskeleton and glomerular filtration barrier.

It is our opinion that screening for *MYH9* risk variants may *eventually* be useful in high-risk populations such as African Americans with close relatives who have ESRD or in those who wish to donate a kidney; however, the high frequency of *MYH9* risk variants in African-derived individuals could render this a less useful screening test. It is important that the additional triggers, or "second hits," required for initiation of renal disease be identified: Either gene– gene or gene– environment interactions. *MYH9* genotypes may be more useful to clinicians for screening purposes and ultimately for selecting therapies, when second hits are identified. For example, if viral infections or other environmental exposures interact with *MYH9* to produce nephropathy, then immunization against infection or avoidance of exposures may be protective from kidney disease even in those who harbor risk variants. At present, novel therapies for slowing or preventing *MYH9*-associated nephropathy and use of *MYH9* genotypes for screening purposes require further study.

Conclusions

Genetic methods have contributed to the detection of a newly recognized spectrum of related kidney diseases. *MYH9*-associated nephropathy is clearly the most common form of CKD in African Americans.

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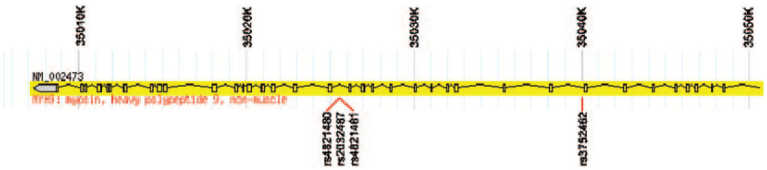

Figure 1.

MYH9 structure and location of the E-1 haplotype SNPs. The first 40 kb of *MYH9*, with exons in boxes and the promoter regions in gray, is shown. The location of the four SNPs that make up the E-1 haplotype are indicated. Gene structure was developed using Haploview ([52]) with infotrack downloaded from http://www.hapmap.org.

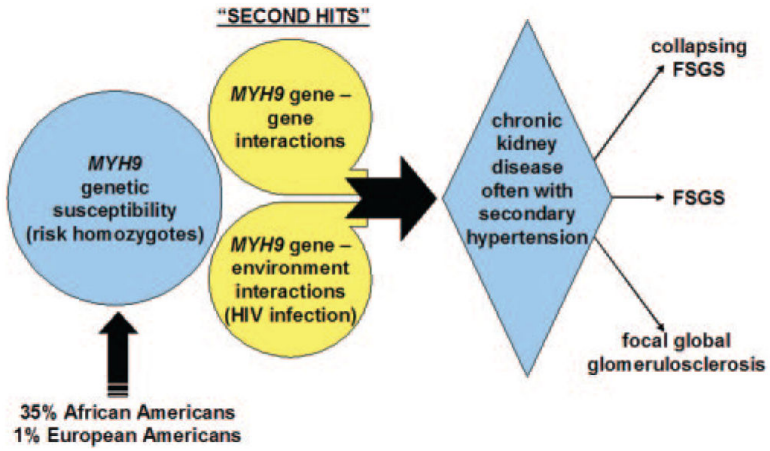

Figure 2.
Proposed pathogenesis of *MYH9*-associated nephropathy.

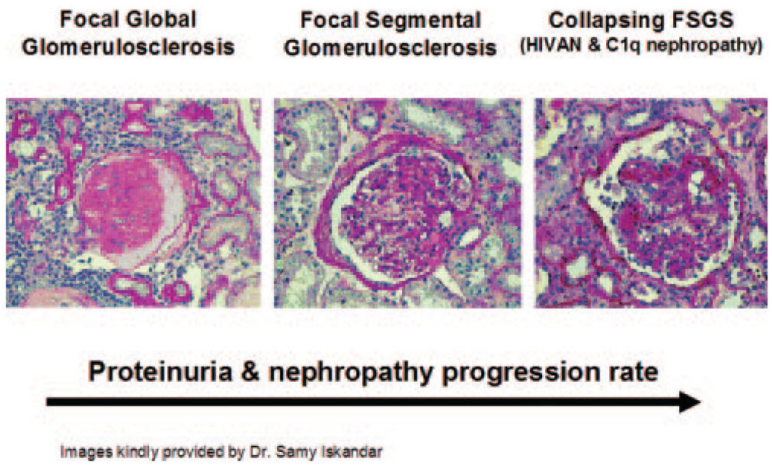

Figure 3.
The spectrum of *MYH9*-associated nephropathy.

Table 1

Issues under investigation in *MYH9*-associated nephropathy

Clinical
value of genetic screening to identify individuals who are at risk for future nephropathy
influence of donor genotypes on outcomes after kidney transplantation
potential influence on ethnic differences in outcomes after dialysis initiation
assessment of renal histology: variants in FSGS on the basis of genotype lesions in African Americans with clinically diagnosed diabetic nephropathy
detection of environmental co-factors that may interact to initiate renal disease
determine natural history of disease and effect on rates of nephropathy progression
determine response to conventional and novel therapies for FSGS and related disorders
Basic
identify the disease-causing polymorphism(s)
determine mechanisms of podocyte injury, and develop preventive therapies
detect additional genes that interact to initiate renal disease
identify the factor(s) on the African continent that selected for nephropathy risk variants