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MYH9 Genetic Variants Associated With Glomerular Disease: What Is the Role for Genetic Testing?

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Summary

Genetic variation in *MYH9*, encoding nonmuscle myosin IIA heavy chain, has been associated recently with increased risk for kidney disease. Previously, *MYH9* missense mutations have been shown to cause the autosomal-dominant *MYH9* (ADM9) spectrum, characterized by large platelets, leukocyte Döhle bodies, and, variably, sensorineural deafness, cataracts, and glomerulopathy. Genetic testing is indicated for familial and sporadic cases that fit this spectrum. By contrast, the *MYH9* kidney risk variant is characterized by multiple intronic single nucleotide polymorphisms, but the causative variant has not been identified. Disease associations include human immunodeficiency virus-associated collapsing glomerulopathy, focal segmental glomerulosclerosis, hypertension-attributed end-stage kidney disease, and diabetes-attributed end-stage kidney disease. One plausible hypothesis is that the *MYH9* kidney risk variant confers a fragile podocyte phenotype. In the case of hypertension-attributed kidney disease, it remains unclear if the hypertension is a contributing cause or a consequence of glomerular injury. The *MYH9* kidney risk variant is strikingly more common among individuals of African descent, but only some will develop clinical kidney disease in their lifetime. Thus, it is likely that additional genes and/or environmental factors interact with the *MYH9* kidney risk variant to trigger glomerular injury. A preliminary genetic risk stratification scheme, using 10 single nucleotide polymorphisms, may estimate lifetime risk for kidney disease. Nevertheless, at present, no role has been established for genetic testing as part of personalized medicine, but testing should be considered in clinical studies of glomerular diseases among populations of African descent. Such studies will address critical questions pertaining to *MYH9*-associated kidney disease, including mechanism, course, and response to therapy.

Keywords

Focal segmental glomerulosclerosis; HIV-associated nephropathy; hypertensive nephrosclerosis; chronic kidney disease; end-stage kidney disease; African American

Recently, admixture mapping was performed in African Americans with focal segmental glomerulosclerosis (FSGS) and human immunodeficiency virus-associated collapsing glomerulopathy (HIV-CG), seeking to identify an African-origin genetic variant that would explain the increased prevalence of these glomerulopathies among individuals of African

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The National Institutes of Health, together with all three authors, has applied for a patent on *MYH9* SNPs associated with the diseases described here.

descent.¹ An admixture peak on chromosome 22 was identified, with the gene *MYH9* at the top of the peak. Confirmatory studies showed that the admixture signal was entirely explained by intronic single nucleotide polymorphisms (SNPs) lying in the middle of the gene. Independently, another research group had performed an admixture scan of non-diabetic end-stage kidney disease (ESKD) and also had identified a chromosome 22 peak; we shared with these colleagues the identification of *MYH9* as the gene responsible for this admixture peak and linkage to *MYH9* was confirmed in this distinct patient population.² Further work by Freedman et al³ has confirmed an association with hypertension-attributed ESKD, and extended the association to hypertension-attributed microalbuminuria⁴ and diabetes-attributed ESKD.⁵ A summary of the data from these reports, presenting the odds ratios for *MYH9* kidney risk variant homozygotes compared with *MYH9* nonrisk variant homozygotes (ie, the recessive model) is presented in Figure 1.

OVERVIEW OF MYOSIN II BIOLOGY AND GENOMICS

Comparative genomics suggests the common ancestor of all living organism, living 3 billion years ago, had about 400 genes, one of which encoded ancestral actin.⁶ Today, prokaryotes have actin-like molecules, whereas all eukaryotic cells have actin, part of a complex cytoskeleton, and, in most instances, myosins. Myosin are cell motors, either traveling along actin filaments or alternatively generating force on actin filaments while remaining in a fixed location. Myosin functions include organelle transport (eg, nucleus, mitochondria, trans-Golgi network, vacuoles, and peroxisomes), cytokinesis (cell division after nuclear division), locomotion, generation of cell tension, and maintenance of cell shape.

Myosin molecules are hexamers, comprising two heavy chains (isoform specific), two essential light chains, and two regulatory light chains. The myosin heavy chain has two functional units: (1) a head domain that binds actin, has adenosine triphosphatase activity, generates force via the motor subdomain, and includes a short neck subdomain that binds the two pairs of light chains, and (2) a long helical (coiled-coil) rod domain that provides stability and is terminated by a short terminal nonhelical tail that promotes homophilic assembly of myosin units and may bind intracellular cargo (Fig. 2). Myosins have been classified into 18 classes based on evolutionary phylogeny of the motor domain.⁷ The largest class is myosin II; this includes both the classic myosins of skeletal, cardiac, and smooth muscle, which are responsible for muscle contraction, and the non-muscle myosins. This latter group is expressed in all nucleated cells of higher organisms (including within muscle, despite the name). Mammalian nonmuscle myosin II molecules comprise three isoforms, A, B, and C; the unique heavy chains are encoded by *MYH9*, *MYH10*, and *MYH14*, respectively. *MYH9* spans 110 kb of genomic sequence, with 41 exons (or 40 exons if the first noncoding exon is excluded). The main RNA transcript is 7.5 kb in length, encoding a protein of 960 amino acid residues.

Cultured podocytes are known to express myosin IIA and IIB.^{8,9} Saleem et al⁹ reported that differentiation of cultured podocytes is associated with up-regulation of a number of components of the actin-myosin complex (although neither *MYH9* nor *MYH10* was noted to be among the up-regulated genes), and angiotensin II stimulates podocyte contractility and decreases monolayer resistance, presumably reflecting contraction. These investigators proposed that although glomerular afferent arteriolar myogenic activity limits the transmission of systolic blood pressure to the glomerular capillary, it is the function of the podocyte to maintain a constant glomerular capillary pressure. In the model, podocytes relax during diastole and contract during systole, to limit capillary expansion and contraction during the cardiac cycle and thereby maintain a constant ultrafiltration rate. If this model is correct, then an intact actin-myosin contractile apparatus is critical to maintaining normal glomerular function.

AUTOSOMAL-DOMINANT *MYH9* SPECTRUM SYNDROMES

These disorders, associated with missense mutations (altered amino acid) or nonsense mutations (premature stop codon) in *MYH9*, represent a spectrum of disorders, including May-Hegglin anomaly (OMIM 155100) and Epstein (OMIM 153650), Fechtner (OMIM 153640), and Sebastian (OMIM 606249) syndromes, as well as isolated sensorineural deafness (OMIM 603622). There is no generally accepted term for this spectrum. Although *large platelet syndrome* has been applied, this term risks confusion with the giant platelet syndrome (Bernard-Soulier syndrome, caused by mutations in genes that encode the platelet glycoprotein 1b). Another proposed term is *MYH9-related disease*,¹⁰ but the recent identification of an association of *MYH9* intronic SNPs with kidney disease, as discussed earlier, makes this terminology problematic. Here we will use the term *autosomal-dominant MYH9* (ADM9) spectrum disorders.

ADM9 spectrum disorders consistently manifest thrombocytopenia, most typically in the range of 40,000 to 80,000 cells/mm³. Platelet function is hypernormal and these patients do not have a bleeding diathesis. Platelets express only the myosin IIA isoform, and this likely explains the defective cytokinesis, the process of cell division, when *MYH9* is mutated. Neutrophils manifest azurophilic Döhle-like inclusions, which represent aggregates of abnormal myosin protein. Patients may have bilateral sensorineural deafness or may have normal hearing. Cataracts may be present.

Kidney abnormalities, seen in Epstein and Fechtner syndromes, include microscopic hematuria with or without proteinuria, which may be subnephrotic or nephrotic; patients may progress to ESKD. Few renal biopsies from ADM9 spectrum patients have been reported, particularly early in the course of renal disease. In a biopsy performed in a patient upon pre-sentation with nephrotic syndrome, light microscopy was normal and focal and segmental podocyte foot process effacement was noted on electron microscopy.¹¹ Although some descriptions note glomerulonephritis, the degree of glomerular proliferation is unclear and the possibility remains that these individuals may manifest largely or exclusively FSGS or its variants. The combination of glomerulopathy, sensorineural deafness, and in some cases cataracts may mimic Alport syndrome, but the other features (particularly abnormal platelets and the autosomal-dominant mode of inheritance) should aid in the clinical distinction.

Importantly, different individuals with the same *MYH9* mutation (eg, R702C) may manifest different subsets of these abnormalities, illustrating that the ADM9 disorders are indeed a spectrum.¹⁰ As shown in Figure 2, ADM9 spectrum mutations have been found in the head domain and the coiled-coil rod domain, including the nonhelical tail domain. Kidney disease has been reported in each of these domains, specifically in association with mutations in exons 1, 16, 24, 25, 26, 30, 37, 38, and 40.¹² It remains unclear whether ADM9 syndrome mutations act via haploinsufficiency or via generation of dominant-negative proteins.

DEFINING THE *MYH9* KIDNEY RISK VARIANT

Importantly, the *MYH9* kidney risk variant is identified by a number of SNPs, all of which are intronic and all of which are in linkage disequilibrium with each other. Sequencing the entire gene among 40 individuals (FSGS and HIV-associated nephropathy [HIVAN] cases and controls), including all 40 exons, the 5' region, the 3' region, and all introns excluding the large first intron, has failed to identify any mutations in the exons that correlate with kidney disease, although a number of additional SNPs were identified that also were associated with the same kidney disease.¹³ Thus, the causative SNP or SNPs remain to be identified and the mechanism of disease remains unknown. Plausible possibilities include

alternative splicing (perhaps specific to the podocyte), altered messenger RNA half-life, and altered micro-RNA putatively located within an intron.

Initially, we proposed that the *MYH9* kidney risk variant is best defined as an extended haplotype (termed *E-1*), defined by 4 SNPs located in introns 13 and 23, using a nomenclature that assigns the first coding exon as exon 1.¹ The *E-1* haplotype is defined as alleles G, C, C, and T at SNPs rs4821480, rs2032487, rs4821481, and rs3752462, respectively. The first three of these SNPs, falling in intron 23, are in near-absolute linkage disequilibrium. Therefore, typing one of these three SNPs, along with rs3752462 (located in intron 13?), allows inferring *E-1* with near certainty; the most accurate inference ($\geq 97\%$ certainty) is given by using rs4821481 and rs3752462. Table 1 gives inferences for haplotypes *E-1* through *E-5* based on typing of these two SNPs. Without doubt, the definition of the *MYH9* kidney risk variant will continue to evolve.

MYH9 RISK VARIANT: ESTIMATES OF KIDNEY DISEASE RISK

We wished to provide some quantitative estimates of the clinical implications of *MYH9* risk variants. To do this, we needed to first estimate the lifetime risk for HIVAN, FSGS, and hypertension-attributed ESKD among African Americans. We gathered information on disease incidence (which requires certain assumptions, as discussed later, because there is no national registry for these diseases in the United States or in other countries) and calculated lifetime risks using a contingency table for each disease, assuming an 80-year lifespan and assuming that current incidence rates continue unchanged in the future. Confidence intervals were extrapolated from the binomial confidence interval for disease occurrence in epidemiologic studies.

First, we estimated the lifetime incidence of HIVAN among individuals of African descent in the United States, in the absence of antiretroviral therapy at 10%, based on an autopsy series from Texas¹⁴ and a pediatric cohort study from Miami.¹⁵

Second, for FSGS, US Renal Data System data for 2007 and prior years indicate that approximately 1,000 cases of incidence FSGS occur annually among African Americans. The incidence of FSGS appears to have increased over the past 2 decades in the United States and elsewhere, as reviewed previously.¹⁶ We conservatively assume that the present incidence remains stable during the lifetimes of African Americans alive today. Life-table analysis predicts 80,000 cases of FSGS ESKD among the 37 million African Americans in the US population at present,¹⁷ indicating a lifetime risk of FSGS ESKD of 0.2% for these individuals. Data from renal transplant centers suggest that approximately 50% of individuals with ESKD, excluding those with diabetes or cystic kidney disease, undergo a kidney biopsy and data from case series suggest that 50% of patients with FSGS reach ESKD by 10 years.¹⁸ We lack data to know whether these are reliable guides for FSGS among African Americans; thus, we do not know if these individuals frequently may manifest subnephrotic proteinuria, making kidney biopsy less likely, or whether it is more or less likely to progress to ESKD than other forms of FSGS. Nevertheless, if we assume that 50% of FSGS cases among African Americans remain undiagnosed by kidney biopsy, and that 50% of FSGS cases among African Americans do lead to ESKD before death from competing causes, then the lifetime risk for FSGS ESKD is 0.8% for these individuals (1 in 125 African Americans).

Third, we estimated lifetime risk for hypertension-attributed ESKD, because there are data available for this diagnosis, and made no attempt to estimate risk for hypertensive nephrosclerosis in general. The most recent US Renal Data System data indicate that in 2007 there were 11,244 African Americans with incident hypertension-attributed ESKD.¹⁹ This

represents a lifetime risk of 2.25% among the 39.7 million African Americans in the US population.

By using these lifetime risk estimates and the odds ratios for HIVAN (8), FSGS (6), and hypertension-attributed ESKD (2.2), we have calculated attributable risk and explained fraction. *Attributable risk* is defined as the reduction in disease incidence that would be observed if the exposure (in this case, the *MYH9* kidney risk variant) were absent, compared with the actual incidence rate. *Explained fraction* is defined as the proportion of disease risk among a population that is entirely explained by a particular variable, among all the genetic, environmental, stochastic, and other determinants of disease. As shown in Table 2, attributable risks for individuals with two *MYH9* kidney risk variants are 59% for HIVAN, 56% for FSGS, and 20% for hypertension-attributed ESKD, whereas explained fractions are 10%, 4%, and 1%, respectively. Similarly, attributable risks for individuals with one or two *MYH9* kidney risk variant are 100% for HIVAN, 72% for FSGS, and 38% for hypertension-attributed ESKD, whereas explained fractions are 12%, 5%, and 2%, respectively. In summary, the attributable fractions are very high, particularly for these relatively common diseases, and this result is driven both by the high odds ratios for disease and high population frequency of the kidney risk variant. On the other hand, the explained fractions are much lower than attributable risks, indicating that other genetic or environmental factors, possibly together with chance, contribute to determining the likelihood of disease in a given individual.

We next computed the estimated lifetime risks, with 95% confidence intervals, for HIVAN, FSGS, and hypertension-attributed ESKD for individuals with 0, 1, and 2 *MYH9* kidney risk variants (Table 3). Thus, for individuals with two *MYH9* kidney risk variants, the lifetime risks are estimated as follows: HIVAN, 20% (1 in 5 persons); FSGS, 1.6% (in 62 persons); and hypertension-attributed ESKD, 3.1% (1 in 32 persons).

MYH9 GENETIC TESTING IN CLINICAL SETTINGS

As noted earlier, the causative SNP(s) or other genetic variant has not been identified and currently identification of the *MYH9* kidney risk variant involves testing at least two SNPs in linkage disequilibrium with the causative variant(s). What is the role for genetic testing? There are no prospective studies on which to base recommendations; we offer our perspectives and opinions.

HIV-1 Infection

Notably, although 100% of HIV-CG patients have one or two copies of the *MYH9* kidney risk variant, 76% have two copies and 0% have zero copies (ie, these individuals appear to be completely protected from HIV-CG), this compares with 36% and 16%, respectively, of the general African American population. Although African Americans who are homozygous for the *MYH9* nonrisk variant appear to be protected against developing HIVAN, they are still susceptible to other renal diseases, including those related to HIV (tubular toxicity of antiretroviral medication, thrombotic microangiopathy, and so forth) and those unrelated to HIV (diabetic nephropathy, hypertensive nephrosclerosis). Our recommendation would be *MYH9* testing only in the context of clinical studies and appropriate screening for kidney disease at least annually, as has been recommended.²⁰

FSGS

Our estimates are that among *MYH9* kidney risk variant homozygotes, the lifetime risk for FSGS is 1.6% (confidence interval, 1.4–1.8), or 1 in 62 individuals. Should we consider identifying and screening high-risk individuals, however that group is defined? Several issues are relevant here. First, how would we screen? We do not know whether these

individuals go through an asymptomatic phase of microalbuminuria or overt proteinuria; if this were the case, then periodic urine protein measurements might detect presymptomatic disease. Second, what would we do if we identified at-risk individuals at screening? We do not know whether particular therapies, such as angiotensin pathway antagonists (including renin inhibitors, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and aldosterone-receptor antagonists) and/or intensive blood pressure control (eg, a target blood pressure of 130/80 mm Hg) might slow progression of proteinuria once it was detected at screening. Third, at what age would we start screening and how long should the screening periods be? If most *MYH9*-associated FSGS appeared after the teenage years (and this remains to be shown), the screening might begin in the late teenage years (while the child is receiving regular pediatric care). Fourth, what are the medical, economic, social, and psychological implications of a screening program that potentially would include a substantial fraction of the 39.7 million African Americans, or 14 million individuals? These are important questions that will require prospective studies and careful thought from all stakeholders before informed decisions can be made.

How does a lifetime FSGS risk of 1.6% among *MYH9* kidney risk variant homozygotes compare with risks for other serious illnesses for which screening is part of standard medical practice? The lifetime risk of breast cancer is 12%²¹ and for cervical cancer (in situ and invasive) is 5%.²² In both cases, efficient screening approaches have been devised, effective therapies are available, and prospective studies have proven the clinical benefits of screening particular populations at particular intervals. Clearly, we need a roadmap for research to allow us to gather similar information before *MYH9* genetic screening can enter clinical practice.

Hypertension

There is an increased lifetime risk of hypertension-attributed ESKD, 3.1% among *MYH9* kidney risk variant homozygotes compared with 1.4% among *MYH9* nonrisk variant homozygotes. Because most of individuals with hypertension and kidney disease do not undergo kidney biopsy, it remains unclear whether they had a primary kidney disease (FSGS or focal global glomerulosclerosis) that leads to hypertension, or whether essential hypertension caused more injury in a genetically at-risk kidney. Before these results can be translated into clinical practice, we need better understanding of the role of *MYH9* in early kidney disease attributed to hypertension. Preliminary data from the African American Study of Kidney Disease in Hypertension suggests that *MYH9* kidney risk variants are associated with a greater propensity to develop advanced chronic kidney disease.²³ Further analysis of these data may shed light on differences by genotype in response to higher versus lower blood pressure targets and the use of angiotensin converting enzyme inhibitor versus β -blocker versus calcium channel blocker. Nevertheless, prospective studies of kidney histology in early hypertension-attributed kidney disease and response to therapy, using stratification by *MYH9* genotype, will be needed if we are to determine whether genetic testing has a clinical role to play.

Diabetes-Attributed ESKD

MYH9 has a relatively weak association with diabetes-attributed kidney disease. The next step will be to study such patients early in the disease course, and to determine whether a nondiabetic glomerular disease is present.

CONCLUSIONS

The identification of *MYH9* as a major genetic contributor to chronic kidney disease among African-derived populations has opened a door to understand disease mechanisms that

underlie several kidney disease syndromes. We recommend *MYH9* genotyping in clinical research studies involving these kidney diseases, particularly when individuals of African descent are included, and possibly in other kidney diseases for which a role for *MYH9* variation is plausible. If we are to determine how to translate these research advances into the diagnosis and treatment of these illnesses, which contribute the heavy burden of ESKD, we need well-designed, suitably powered prospective studies of the natural history and response to therapy of *MYH9*- associated kidney diseases.

Recent work suggests that a variation in the gene immediately centromeric to *MYH9*, which is *APOL1*, encoding apolipoprotein L1, accounts for most but not all of the genetic risk for kidney disease in this region of chromosome 22.²⁴ It appears that *APOL1* missense mutations protect against *Trypanosoma brucei rhodesiense* and that recent selection during the past 10,000 years has selected for these variants in the African population. These variants are also more highly correlated with CKD than are *MYH9* risk variants. Nevertheless, a (statistically lesser) role for *MYH9* risk variants in CKD susceptibility has not been excluded, and indeed other loci in this genetic neighborhood may also contribute to CKD susceptibility. Further molecular, cellular and experimental animal work will be required to define the relative contributions of *APOL1*, *MYH9* and other near-by loci to CKD risk. Clearly the identification of *APOL1* variants is a major step forward that will improve the prospects for genetic screening to identify at-risk individuals and will likely facilitate the development of effective prevention and treatment strategies.¹³

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Figure 1.

MYH9 kidney risk variant odds ratios for kidney disease. A comparison of odds ratios, comparing the *MYH9* kidney risk variant homozygote and *MYH9* nonrisk variant homozygotes, for HIVAN, idiopathic FSGS, non-diabetic ESKD, hypertension-attributed ESKD attributable to hypertension, and diabetes-attributed ESKD in four studies cited in the text. Figure reproduced with permission from Kopp et al (Seminars in Nephrology, in press).

Figure 2.

MYH9 protein and exon structure: mutations causing large platelet syndromes. The structures of nonmuscle myosin IIA and IIC are shown; each is a hexamer composed of two heavy chains (encoded by *MYH9* in the case of myosin IIA), two essential light chains, and two regulatory light chains. The location of missense mutations in the myosin IIA molecule associated with autosomal-dominant *MYH9* spectrum disorders are shown.

Table 1Genotyping to Define the *MYH9* E-1 Risk Allele

rs4821481	rs3752462	<i>MYH9</i> E Haplotype
CC	TT	E-1, E-1
CT	CT	E-1, E-2
CT	TT	E-1, E-3
CC	CT	E-1, E-5
CC	CC	E-5, E-5
TT	CC	X, X
TT	TT	E-3, E-3
CT	CC	E-5, X
TT	CT	E-2, X

NOTE. Genotyping the two SNPs shown allows the E-1 haplotype to be determined with a high degree of confidence ($\geq 97\%$). The other extended (E) haplotypes are shown. In three instances (shown as "X"), the specific E haplotype cannot be determined but the presence of the E-1 haplotype can be confidently excluded.

Table 2Epidemiologic Implications of *MYH9* Kidney Risk Variant Haplotype

	Cigarette Smoking	<i>MYH9</i> Kidney Risk Variants (2 copies)	<i>MYH9</i> Kidney Risk Variants (1 or 2 copies)
Attributable risk	Lung cancer: males, 90%; females, 60%	HIV-CG, 59% FSGS, 56% Hypertension-attributed ESKD, 20%	HIV-CG, 100% FSGS, 72% Hypertension-attributed ESKD, 38%
Explained fraction	Lung cancer, 12%	HIV-CG, 10% FSGS, 4% Hypertension-attributed ESKD, 1%	HIV-CG, 12% FSGS, 5% Hypertension-attributed ESKD, 2%

NOTE. Attributable risk is the proportion of disease incidence that would be removed from the population under consideration if a factor (exposure) were removed. Explained fraction is the proportion of disease incidence that is entirely explained by the factor under study, in the context of all known and unknown genetic, environmental, and stochastic factors that determine which individuals will develop the disease.

Table 3Clinical Implications of the *MYH9* Kidney Risk Variant: Estimates of Lifetime Risk

	Average Lifetime Risk	0 Kidney Risk Variants	1 Kidney Risk Variant	2 Kidney Risk Variants
HIV-CG (without antiretroviral therapy)	10%	0% (0, 6)	5% (3, 8) 1:20	20% (15, 25) 1:5
FSGS	0.8%	0.2% (0.1, 0.4) 1:500	0.4% (0.3, 0.5) 1:250	1.6% (1.4, 1.8) 1:62
Hypertension-attributed ESKD	2.25%	1.4% (1.1, 1.7) 1:71	1.9% (1.7, 2.1) 1:53	3.1% (2.8, 3.3) 01:32

NOTE. Lifetime risks were estimated, as described in the text, for 0, 1, and 2 copies of the *MYH9* E-1 kidney risk variant. Numbers in parentheses are 95% confidence intervals.