Published in final edited form as:

Semin Dial. 2010 ; 23(3): 244–247. doi:10.1111/j.1525-139X.2010.00721.x.

Potential effects of *MYH9*-associated nephropathy on dialysis and kidney transplant outcomes

Barry I. Freedman and Mariana Murea

Department of Internal Medicine, Section on Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Abstract

Several related disorders comprise the spectrum of non-muscle myosin heavy chain 9-associated (*MYH9*) nephropathy. The contribution of variants in this single *MYH9* gene to ethnic differences in the incidence rates of end-stage renal disease (ESRD) is now clearly established. The importance of recognizing the role of *MYH9* in these inherited kidney disorders goes beyond simple disease association; there may well be effects on clinical outcomes in patients on dialysis and after kidney transplantation. *MYH9* may adversely affect treatment outcomes in severe kidney disease and such gene effects are rarely encountered in practice.

Keywords

African American; dialysis; FSGS; kidney disease; *MYH9*; outcomes; transplantation

The impact of the *MYH9* gene on ESRD epidemiology

Although genetic factors impact susceptibility to virtually all diseases, few, if any gene associations in common, complex disorders are as strong as *MYH9* in non-diabetic nephropathy.^{1,2} Risk variants in *MYH9* are associated with several related and often severe forms of kidney disease in African Americans, European Americans and Europeans;^{3,4} apparently not in American Indians.⁵ In addition, *MYH9* is unlikely to be a common cause of nephropathy in East Asians as risk variants are rare in this ethnic group.⁶ The frequency of the *MYH9* E1 risk haplotype in African Americans (60% inherit one copy; 35% are homozygous) far exceeds that in European-Americans (4% inherit one copy; 1% are homozygous). This striking observation accounts for the majority of ethnic variation in incidence rates of non-diabetic ESRD in African-derived individuals, relative to those of European origin.^{1,2}

MYH9 is strongly associated with idiopathic focal segmental glomerulosclerosis (FSGS)^{1,2}, the collapsing variant of FSGS (*e.g.*, Human Immunodeficiency Virus infection and collapsing C1q nephropathy⁷), focal global glomerulosclerosis (FGGS; historically labeled hypertensive nephropathy)^{3,8} and approximately 16% of African Americans with clinically diagnosed type 2 diabetic nephropathy.⁹ It remains unclear whether individuals with diabetes have classic diabetic nephropathy or FSGS with coincident diabetes. *MYH9* also explains the long-standing observation that disparate causes of ESRD cluster in single African American families.^{10,11} It appears unlikely that *MYH9* is associated with lupus nephritis, although this kidney disease disproportionately impacts African Americans.¹²

MYH9 encodes the non-muscle myosin heavy chain 9, a cellular motor responsible for moving actin filaments in cells.^{13,14} Risk variants may result in the development of renal-limited kidney diseases within the spectrum of FSGS and FGGS. It is apparent that African Americans labeled as having “hypertensive nephrosclerosis” (HN), “arteriolar nephrosclerosis” or “hypertensive ESRD”, are often misclassified.^{15,16} Many of these patients have renal-limited lesions such as FGGS or FSGS, likely with secondarily elevated blood pressure. This finding may have implications for ethnic differences in survival on dialysis.¹⁷

Does *MYH9* contribute to improved survival in African Americans on dialysis?

Longer survival after dialysis initiation is consistently observed in African Americans relative to European Americans.^{18,19} This phenomenon occurs despite later referral of African Americans to nephrologists, generally lower socioeconomic status, more limited access to healthcare, and poorer control of conventional cardiovascular disease (CVD) risk factors, including more frequent and severe hypertension and diabetes. How these adverse factors coalesce to yield improved survival rates was unclear.

A number of factors appear to influence ethnic differences in dialysis survival independent from *MYH9*. For example, African Americans have paradoxically lower levels of calcified atherosclerotic plaque in their coronary arteries, carotid arteries and aorta, relative to European Americans; despite presence of more severe conventional CVD risk factors.^{20,21,22,23} In the same way that African Americans appear predisposed to nephropathy, they are relatively protected from the potentially related processes of atherosclerosis (calcified atherosclerotic plaque), osteoporosis, and calcium-containing kidney stones.^{24,25}

The observation that European ancestry predisposes African Americans to greater amounts of calcified atherosclerotic plaque²⁶ suggests that admixture mapping, the methodology that identified *MYH9* as a nephropathy gene, may prove useful in identifying inherited causes of coronary artery calcified atherosclerotic plaque.²⁷ Admixture mapping has the potential to identify genomic regions harboring excess European ancestry in African Americans with high levels of coronary artery calcified plaque; susceptibility variants should more often be present in European-derived individuals. Lower rates of myocardial infarction are observed in African Americans with ESRD.²⁸ Albuminuria is a non-conventional cardiovascular disease risk factor in European Americans with lesser effects in African Americans.^{29,30} The relative protection from atherosclerosis and lack of association between albuminuria and calcified atherosclerotic plaque in African Americans likely contributes to ethnic differences in survival once on dialysis.¹⁷

In addition, *MYH9* appears to be primarily associated with renal-limited forms of non-diabetic kidney disease. African Americans and European Americans who are labeled as having “hypertensive nephropathy” appear to have different disorders. “Hypertensive ESRD” and “HN” in African Americans are often *MYH9*-associated primary kidney diseases. As such, aggressive treatment of hypertension including with angiotensin converting enzyme inhibition, fails to halt progression of nephropathy in African Americans.³¹ Renal biopsy findings in those with HN also differ between ethnic groups, with African Americans having extensive solidified glomerulosclerosis and interstitial fibrosis; European Americans manifest ischemic glomerular collapse resulting from arteriolo-nephrosclerosis.³² The HyperGEN study demonstrated that hypertensive African Americans had similar frequencies of *MYH9* risk variants as the general African American population, lessening the likelihood that hypertension initiates kidney disease.³³ Together, these data reveal that high blood pressure is often a secondary phenomenon in African Americans with primary *MYH9*-

associated nephropathy (FSGS and FGGS). There is likely less systemic atherosclerosis in African Americans with HN, since the kidney disease is renal-limited.

In contrast, European Americans labeled with HN more often have small vessel renal disease that improves with hypertension treatment, lipid lowering and smoking cessation.^{34,35,36} Untreated, this systemic vascular process can progress to ischemic glomerular collapse. As such, European Americans labeled with HN likely have higher rates of co-existing large vessel atherosclerosis. We believe that the lower rates of atherosclerosis may contribute to the improved survival rates seen in African Americans with non-diabetic (and, to a lesser extent, diabetic) etiologies of ESRD.

The impact of donor ethnicity on kidney transplant outcomes

Kidney transplantation is another scenario where ethnicity plays a major role in outcome. Shorter allograft survival is seen when kidneys are donated by African Americans, whether transplanted into European American or African American recipients.³⁷ A satisfactory explanation for the poorer allograft survival in African American donor kidneys is lacking.

It is clear that “second hits”, either *MYH9* gene-gene or *MYH9* gene-environment interactions are required to initiate nephropathy in *MYH9* risk homozygotes.³⁸ While 4% of African American *MYH9* E1 haplotype risk homozygotes develop FSGS, the risk rises fivefold to 20% in those with concomitant HIV infection. However, 80% of HIV infected African American *MYH9* risk haplotype homozygotes do not develop renal disease; therefore, additional susceptibility factors must initiate HIVAN. These second factors may be specific HIV-1 viral component genes or additional environmental exposures (non-HIV viral infections).^{38,39}

We postulate that similar factors may be involved in the poorer allograft survival rates observed in African Americans, as approximately 36% of African American kidney donors are expected to be homozygous for *MYH9* E1 risk variants. As HIV infection is an environmental factor initiating *MYH9*-associated nephropathy, we postulate that the toxic effects of calcineurin inhibition, cold ischemia time and other environmental factors involved in the transplant procedure might play similar roles.⁴⁰ This is an important area for future investigation. It is likely that the diverse genetic profiles in African Americans, coupled with heightened immune responses (particularly among younger African American recipients) also influence transplant outcomes. However, prior to *MYH9*, no powerful common gene variant had been associated with kidney disease.

Conclusions

Polymorphisms in the *MYH9* gene have the potential to impact outcomes in patients with ESRD, both on dialysis and after kidney transplantation. Although additional factors are likely involved in ethnic differences in kidney disease outcome, *MYH9* has several unique attributes. Risk alleles aggregate far more often in African-derived individuals and this gene has a profound effect on susceptibility to several common and related kidney diseases. Patients with CKD, those on dialysis, and those who have (or will) receive kidney transplants may be impacted by *MYH9* gene variants. This exciting breakthrough presents new opportunities for reducing ethnic disparities in kidney disease. Scientists can now attempt to target this gene and its pathway; a reduced burden of chronic kidney disease in African-derived individuals may result.

Acknowledgments

This work was supported in part by NIH grants RO1 DK 070941, RO1 DK 071891, and RO1 DK084149. The authors report no conflicts of interest in this work.

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