

### *Newly-identified Genetic Variations Account for Much of the Increased Burden of Kidney Disease among African Americans*

For the first time, researchers have identified variations near a single genetic locus that are strongly associated with kidney diseases disproportionately affecting African Americans. Two research teams independently studied kidney diseases arising from causes other than diabetes. Kidney disease can lead to kidney failure, requiring long-term dialysis or a kidney transplant to sustain life. Using a type of genome-wide association technique that relies on differences in the frequency of genetic variations between populations, the researchers identified several variations in the region of the *MYH9* gene on chromosome 22 as major contributors to excess risk of non-diabetic kidney disease among African Americans. Somewhat surprisingly, both research teams found no association between the *MYH9*-area variants and diabetes-related kidney failure in this population, a finding that suggests the mechanisms leading to chronic kidney disease and then to kidney failure may be different depending on the underlying cause. This insight may have important implications for the treatment of the very large number of individuals with kidney disease.

#### **Kidney Disease: A Heavy Burden for Some Populations**

Early-stage kidney disease often has no symptoms. Left unchecked, however, it can silently progress to kidney failure, a condition in which the kidneys are no longer able to filter waste and excess fluids from the blood. As many as 26 million U.S. adults over the age of 20 are estimated to have some degree of impaired kidney function,<sup>1</sup> and over a half million Americans were receiving life-sustaining kidney dialysis or were living with a kidney transplant at the end of 2006<sup>2</sup> (the most recent year for which complete data are available). Despite recent advances in preserving kidney function in individuals with early-stage kidney

disease, serious health complications are common. In fact, roughly half of the people with kidney disease will die from cardiovascular disease before their kidney function further deteriorates and they progress to full-blown kidney failure.<sup>3</sup>

The two most common causes of kidney failure are diabetes and hypertension (high blood pressure), which together account for about 70 percent of all new cases.<sup>2</sup> Both conditions are seen more frequently in members of ethnic minorities, and African Americans bear an especially heavy burden of kidney disease. African Americans are nearly 3 times as likely as whites to develop kidney failure from any cause.<sup>4</sup> One such cause is a form of kidney disease called focal segmental glomerulosclerosis (FSGS), in which the glomeruli—the tiny filtering units of the kidneys—are damaged and scarred.<sup>5</sup> Most FSGS arises from unknown causes and is termed “idiopathic” FSGS. African Americans are approximately 5 times more likely to develop idiopathic FSGS compared to individuals of other racial backgrounds. The health disparity increases with HIV infection: African Americans are 18 to 50 times more likely than whites to develop FSGS related to infection with HIV, the virus that causes AIDS.<sup>6,7</sup> These rather striking disparities represent a serious public health problem, not only because of the kidney disease itself, but also because people who have even mild- to moderately-severe kidney disease typically have high blood pressure and other risk factors for serious complications such as cardiovascular disease.<sup>2</sup>

What accounts for this dramatically increased risk of severe kidney disease in African Americans? Scientists and physicians have long known that kidney disease tends to run in families and cluster in ethnic groups. These observations indicate that

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kidney disease is likely to have a genetic component. It is also almost certain that environmental factors play a role in disease susceptibility as well. However, studies that have attempted to identify genes that confer susceptibility to kidney disease and kidney failure have not generally been successful.

Furthermore, it is not clear that all forms of kidney disease originate from a common starting point or progress through a shared pathway. For example, while patients with diabetes or those with hypertension are at increased risk of developing kidney disease and kidney failure, not all patients at risk go on to develop kidney disease. In addition, it is not clear that the underlying disease mechanisms which initiate injury and facilitate progression in diabetic and hypertensive kidney disease are the same. If, in fact, these two conditions cause kidney disease through different pathways, then treatment strategies for people whose kidney disease is a consequence of diabetes could be very different from those for people whose kidney disease is attributed to hypertension. Because of these considerations, it is especially important to identify the genetic contribution to disease development and progression and characterize the biological pathways that lead to diminished kidney function.

### **New Techniques Allow Researchers To Ask New Questions**

For some conditions, mutations in a single gene are sufficient to cause disease, and careful analysis of inheritance patterns in families can often readily identify the gene responsible. These diseases are termed “simple” genetic diseases, because their underlying cause, while not always easy to uncover, tends to lead to disease in a straightforward way.

However, many diseases likely arise not from mutations in a single gene but from the interplay of complex genetic susceptibility—resulting potentially from multiple genes, each of which may have only modest effects—and environmental influences. In the case of these “complex” genetic diseases, identifying

the genetic contribution of multiple, widely-spaced chromosomal regions to disease development and progression can be quite difficult.

Recently, a new technique, termed admixture mapping, has been developed to search for genes that cause complex genetic diseases. Admixture mapping is particularly useful in examining the underlying genetic causes of complex diseases in which the frequency of disease is very different between two populations. Using admixture mapping, scientists examine haplotypes—groups of genes spanning multiple chromosomal loci that are transmitted together. These haplotypes are inherited; therefore, haplotypes tend to be similar among members of the same population but to differ between members of different populations. Admixture mapping takes advantage of the fact that genetic variants that are not linked to one another tend to dissociate from one another rather rapidly—within a few generations—while those that are linked tend to stay together longer. The relatively recent (anthropologically speaking) mixing of European and African populations is referred to as “admixture”: the formation of a new population with a heterogeneous mixture of African- and European-derived haplotypes.

### **A New Window into the Genetics of Kidney Disease**

Because of the striking difference in kidney disease and kidney failure rates between whites, who are largely of European ancestry, and African Americans, researchers had speculated that admixture mapping might be an effective way to try to identify which chromosomal regions are associated with the development of kidney disease. The rationale behind these experiments was that chromosomal regions that confer an increased risk of kidney disease would be more common in individuals of African ancestry than in those of European ancestry. At least two groups of scientists hypothesized that, by using admixture mapping, they could identify genetic variants that tracked closely with disease development.

In the fall of 2008, the two research teams reported

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the identification of genetic variants more common in African Americans that seemed to explain a large proportion of the excess burden of FSGS and HIV-associated and other non-diabetic kidney disease in African Americans. In addition, the contribution of this genetic variation to an individual's risk of developing kidney disease is higher than that observed for nearly all previously described genetic factors discovered by genome-wide scans, including those for prostate cancer, diabetes, cardiovascular disease, breast cancer, and hypertension.

One research team, which included members of the NIDDK Intramural Research Program's Kidney Disease Branch and other researchers, studied individuals with FSGS, HIV-associated FSGS, and hypertensive end-stage kidney disease. The other team, consisting of researchers working as part of the NIDDK-funded Family Investigation of Nephropathy and Diabetes Consortium, was led by researchers at The Johns Hopkins University and included collaborating scientists at other institutions. They examined patients with kidney failure arising from multiple causes, including diabetes, hypertension, FSGS, and HIV infection. Using admixture mapping, both groups of scientists identified a genetic variant in a region of chromosome 22 that correlated strongly with susceptibility to certain kidney diseases.

Fine mapping of this chromosomal region revealed that the gene *MYH9* was located in the identified area. *MYH9* encodes the protein “non-muscle myosin heavy chain 9,” which is part of non-muscle myosin IIA. Myosin is a protein made up of several subunits and serves as a cellular motor, providing the force for cell movement, cell tension, and cell division. The most common form of myosin is found in skeletal muscle and is involved in muscle contraction. Non-muscle myosin IIA is a form of myosin found in many tissues, including—despite its name—muscle. The *MYH9* gene is expressed in podocytes, specialized cells within kidney glomeruli

that play an important role in the filtering of waste and excess fluid. Podocyte damage is a hallmark of FSGS and other kidney diseases that can lead to reduced kidney function and/or kidney failure. However, it is not known how variations in the *MYH9* region might impact podocyte function.

The degree to which these genetic variants increase risk of developing kidney disease in African Americans from certain causes is truly striking. *MYH9* risk variants account for nearly all of the increased risk for idiopathic FSGS and HIV-associated FSGS among African Americans compared to European Americans and a portion of the increased risk for hypertensive kidney disease. Surprisingly, however, these variants were not associated with kidney failure arising from diabetes.

The risk of developing kidney disease is strongest when an individual has two copies of the risk variant. Nonetheless, even among individuals with two risk variants, kidney disease is uncommon. Thus 36 percent of African Americans have two copies of the risk variant but only approximately 1 in 50 of these individuals will develop FSGS during the course of a lifetime. It is likely other factors, possibly additional genes or environmental influences, are important in triggering FSGS. Future research efforts will focus on the identification and characterization of these additional factors.

It is important that it is the presence of the variant that confers the increased risk of kidney failure, not African ancestry *per se*. However, these variants were much more frequently seen among people of African ancestry than among those of European ancestry—60 percent of alleles among African Americans are the risk variant (84 percent of African Americans carry one or two copies of the risk allele), while only 4 percent of alleles among European Americans are the risk variant (8 percent of European Americans carry one or two copies of the risk allele).

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### Implications and Future Directions

Although both studies described here implicate variations in the chromosomal region surrounding *MYH9* as important risk factors for kidney disease, scientists have not identified specific mutations in the *MYH9* gene that might suggest a causal mechanism. One possibility is that the critical genetic variations lie not within the coding sequence of the *MYH9* gene, but in the surrounding chromosomal regions. The nature of these hypothetical variations, and the ways they might alter cellular metabolism or function so as to confer greater risk of non-diabetic kidney disease, are the subject of ongoing investigations. Future studies will aim to characterize the exact nature of the variations in the *MYH9* region and how these variations may influence susceptibility to non-diabetic kidney disease. Additional future studies will focus on the pattern of *MYH9* expression across tissues, and investigation into the role played by *MYH9* in podocyte function, and how this might be disrupted in individuals carrying the risk variant.

One of the central questions facing researchers who study kidney disease is whether all kidney disease is created equal: although many different conditions—diabetes, hypertension, and FSGS were among the ones studied by these investigators—put people at increased risk for chronic kidney disease and kidney failure, it is not known whether these conditions share a common disease pathway or each have unique characteristics that define them. This distinction is important, because current approaches to therapy are aimed at preserving kidney function and addressing the underlying health problem, not at addressing specific processes that may damage the kidneys. The discovery that a particular genetic variation confers susceptibility to kidney failure by some mechanisms—such as hypertension and FSGS—and not by others—such as diabetes—indicates that there are likely at least two pathways to kidney failure.

These findings also validate the use of admixture mapping to perform genome-wide scans to identify susceptibility genes for complex diseases. Insights gained from the studies have important implications for improved patient care and for understanding the basic biology of kidney disease and kidney failure.

Finally, this story highlights the importance of collaborations between scientists at the NIH and NIH-funded investigators at outside research institutions. Government-academic collaborations of this kind are one way to move translational research forward, from the bench to the bedside and beyond, and provide the knowledge base for developing new therapies for chronic health disorders such as kidney disease and kidney failure.

*The investigators in the NIDDK Intramural Research Program, who first identified the MYH9 gene as contributing to kidney disease, have been conducting basic and clinical research studies of kidney disease, focusing on focal segmental glomerulosclerosis, at the NIDDK since 1995. Scientists at the National Cancer Institute's Center for Cancer Research also contributed to this study. The Johns Hopkins-led research team, that confirmed and extended the MYH9 findings, is part of the NIDDK-funded Family Investigation of Nephropathy and Diabetes (FIND) Consortium. First funded in 1999, the Consortium was established to identify genetic pathways that may be critical for the development of diabetic kidney disease as well as to identify candidate genes and/or pathways that may be amenable to therapeutic strategies to prevent the onset or progression of kidney disease. Though originally conceived as an effort to identify genes associated with diabetes-related kidney disease, FIND investigators discovered an important clue regarding non-diabetic kidney disease. The two studies were published in the journal Nature Genetics in October 2008; the citations are Nat Genet 40: 1175-1184, 2008 and Nat Genet 40: 1185-1192, 2008.*

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<sup>3</sup> Kundhal K and Lok CE: Clinical epidemiology of cardiovascular disease in chronic kidney disease. *Nephron Clin Pract* 101:c47-c52, 2005.

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<sup>7</sup> Eggers PW and Kimmel PL: Is there an epidemic of HIV infection in the US ESRD program? *J Am Soc Nephrol* 15: 2477-2485, 2004.