

Risky Business:

MYH9 Risk Variants Explain Increased Burden of Kidney Disease among African-Americans

Chronic kidney disease affects more than one in ten individuals in the United States alone, either due to specific kidney disorders such as focal segmental glomerulosclerosis (FSGS) or in association with other illnesses such as diabetes, hypertension, lupus, and HIV. Tracking the genes involved in kidney disease, as with any complex disease, can be challenging—in the case of FSGS, for example, over 10 genes have been previously associated, but their polymorphisms explain only a small portion of the disease burden.

In the October 2008 issue of *Nature Genetics*, Cheryl Winkler, Ph.D., Head of CCR's Molecular Genetics Epidemiology Section, and her colleagues identified—for the first time—variations in a single gene that are strongly associated with kidney diseases. Knowing that these diseases disproportionately affect African-Americans, Winkler and her colleagues relied on admixture mapping to increase the power of their genetic analyses

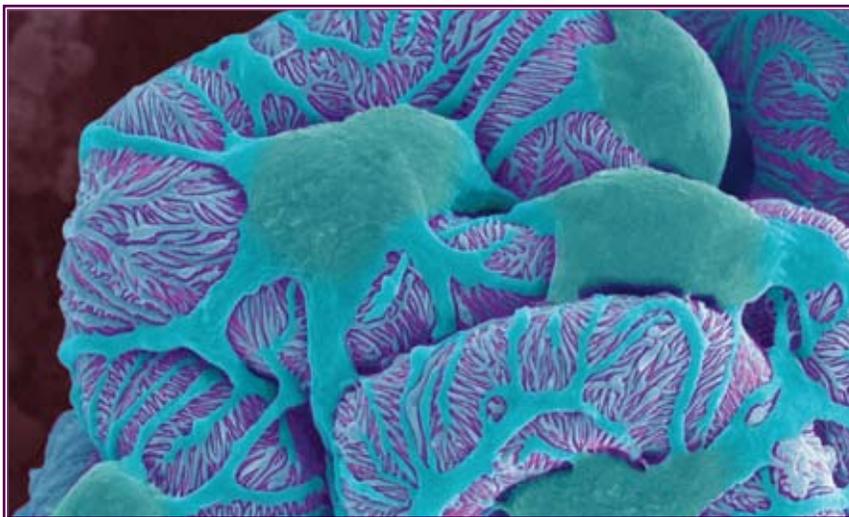
substantially. Based on the hypothesis that risk alleles are present at higher frequency in persons of African descent as compared to European descent, the researchers were able to confine their search to regions of the genome where individuals with the disease have relatively more African ancestry. Using this method followed by fine positional mapping of the candidate gene, they identified several variations in the *MYH9* gene that contribute to

FSGS, HIV-associated nephropathy, and nondiabetic kidney failure.

Their findings reveal that risk among African-Americans with these variants is increased more than four-fold for FSGS, more than six-fold for HIV-associated FSGS (HIVAN), and more than double for nondiabetic kidney failure. About 60 percent of African-Americans carry the risk variants in contrast to less than 3 percent of European-Americans. This large disparity led Dr. Winkler and her team to the conclusion that the increased burden of kidney diseases—especially of FSGS and HIVAN—among African-Americans is substantially due to *MYH9* risk alleles. However, the specific causal variants have not yet been identified.

MYH9-associated kidney disease involves injury to podocytes, cells in the kidney glomeruli (tiny tufts of capillaries that carry blood within the kidneys) that form one of three filtration barriers in the kidney. *MYH9* defects likely produce podocytes that are more susceptible to injury; thus, in the event of a secondary hit (via viral infection, environmental toxins, or other disease), kidney disease develops more easily. In contrast, chronic kidney disease associated with diabetes does not show an association with *MYH9* and may, therefore, be of distinct mechanistic origin.

“This is a finding with excellent bench-to-bed potential—for targeted drug therapy, genetic screening, screening potential donor kidneys, and improved diagnostic decision trees,” said Dr. Winkler. With such a strong risk association, physicians should soon be able to genetically screen patients to identify at-risk individuals and implement preventive measures, including modifiable risk reduction.



(Image: Dennis Kunkel Microscopy, Inc.)

A scanning electron micrograph of a normal podocyte showing the cell body and foot processes surrounding a capillary that forms the kidney glomerulus—the primary blood filtration unit. Kidney diseases associated with *MYH9* are characterized by changes in podocyte structure and glomerular scarring.

To learn more about Dr. Winkler's research, please visit her CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=winkler>.