ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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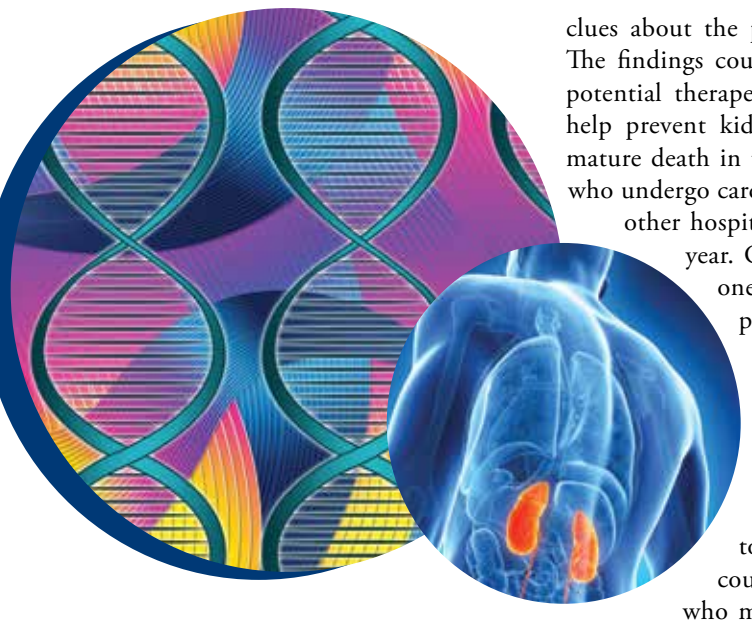
Genetic Markers Could Help Identify Hospital Patients at Risk for AKI

By Kurtis Pivert



Researchers have isolated several genetic markers that could help identify individuals at risk for acute kidney injury (AKI) in the hospital setting (1). Results from the study presented at ASN Kidney Week 2014 in Philadelphia, PA, offer new clues about the pathogenesis of AKI. The findings could eventually lead to potential therapeutic interventions to help prevent kidney failure and premature death in thousands of patients who undergo cardiovascular surgery or other hospital interventions each year. Currently, AKI affects one in five hospitalized patients worldwide.

Collaborators from Yale University, Vanderbilt University, and the University of Western Ontario wanted to determine if they could identify patients who may have a higher genetic risk for developing AKI in the hospital. Doing so could uncover novel pathways that could be targeted for therapeutic interventions, said senior author Chirag R. Parikh, MD, PhD, FASN of Yale.

Investigators in this multicenter study weren't alone in their clinical suspicion that some individuals could have a genetic predisposition for developing AKI in the hospital setting. "What is clear is that patients of similar age and health status can have drastically different kidney outcomes after a potential insult like cardiopulmonary bypass surgery," said Benjamin Humphreys, MD, PhD, FASN, of Brigham and Women's Hospital and Director of the Harvard Stem Cell Institute Kidney Group in Boston. "Many patients do just fine, but others develop AKI. The absence of obvious clinical factors to explain these divergent outcomes suggests a role for genetic predisposition."

Until recently, analysis methods limited the scope of genetic AKI studies. "The putative genetic components of AKI have until recent years been mainly investigated by hypothesis-driven research (of candidate genes)," Parikh said. "But technological progress in genotyping has opened the possibilities

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Most Americans Aren't Healthy Enough to Be Kidney Donors

Just over half of adults in the United States—including nearly two-thirds of African Americans—have health conditions that would preclude their becoming living kidney donors, according to a study presented at Kidney Week 2014.

Anthony J. Bleyer, Jr., and colleagues of Wake Forest School of Medicine, Winston-Salem, NC, performed a population-based study to estimate the percentage of Americans healthy enough for kidney donation. The analysis included data on adults aged 21 to 70 years, drawn from The National Health and Nutrition Examination Survey 2010–2011. The investigators studied the presence of common factors that are used to exclude volunteers from donating a kidney in a representative sample of the United States population.

They found that 55.2 percent of the United States population would be ineligible to donate a kidney because of health conditions. A history of hypertension, the most common excluding condition, was present in 19.2 percent of participants. This was followed by obesity, 15.0 percent; excessive alcohol intake (more than four drinks per day), 11.6 percent; and diabetes, 11.5 percent.

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The rates of medical ineligibility were higher at lower levels of household income: 60.1 percent of individuals with an income below $35,000 would be unable to donate, versus 49.3 percent with an income above $100,000.

Financial pressures and immigration status are nonmedical factors that often affect the ability to be a kidney donor. With the addition of income below the poverty line and non–United States citizenship, 68.5 percent of the United States population would be ineligible to donate. The figure rose to 75.8 percent after the exclusion of smokers and of individuals with shortness of breath when walking up an incline.

There were significant racial and ethnic differences in the distribution of exclusionary medical conditions, with African Americans having the highest rates of obesity, hypertension, diabetes, and microalbuminuria. Overall, 63.9 percent of African Americans would be ineligible to donate, compared with 54.8 percent of whites.

There is a well-recognized shortage of living kidney donors in the United States. The new report is the first population-based study to evaluate the rates of specific medical conditions and social factors that would exclude individuals from living kidney donation.

"It is well known that African Americans and individuals with lower incomes are at an increased risk of kidney failure. Unfortunately, their potential donors—who are very likely to come from the same social groups—are also much less likely to be kidney donors due to comorbid conditions," said Anthony Bleyer, the senior investigator in the study. "Increasing the number of living donors will require addressing this important issue."

Increasing obesity and worsening health of the general population decrease the pool of potential donors. "Financial compensation for time lost at work and lost income would likely improve the ability to donate in 36.1 percent of the eligible donor pool that has an adjusted family household income of less than $35,000," Bleyer said.

Passing the Torch

By Pascale H. Lane

Six years ago *ASN Kidney News* did not exist. The magazine came to life in January 2009. Over the years it has grown and developed, much like a child. Despite some early stumbles and falls, it has now learned to walk and talk and live.

As with my own children, *ASN Kidney News* has matured and readied itself to live without me. I know our new editor-in-chief, Richard Lafayette, MD, FACP, will help it mature further; however, I will miss my baby just the same. I have learned so much from this job, and it has provided me hours of joy (and some frustration) over the past six years.

This swan song would be incomplete without expressing my thanks to a number of people. First, the editorial advisory board provided inspiration and ideas for content and features. Next, I must thank those who wrote and edited articles and feature sections. I know many of you performed these tasks at least somewhat reluctantly, but your efforts made the magazine successful. I must thank the executive editor, Dawn McCoy. She will be continuing in her role, but I will miss our calls. I must also thank *Kidney News* designer Lisa Cain, who conceived the magazine's original design and continues to work wonders with each monthly issue.

Finally, I want to encourage all members of the American Society of Nephrology to get involved in its efforts. The organization does a lot for us, but it needs the input and energy of its members to get it right. Volunteer for a group or committee. Sign up for political action alerts. And always read *ASN Kidney News*.

Pascale H. Lane, MD, FASN, is the outgoing editor-in-chief of ASN Kidney News. *She will remain on the* KN *Editorial Advisory Board.*

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toward hypothesis-generating genomic screens and novel opportunities to explore polygenetic perspectives, now spanning a wide array of possible analyses falling under the term Genome-Wide Association Study (GWAS)."

With GWAS scientists can analyze genetic variants in multiple individuals to determine if a disease or trait is linked to any single-nucleotide polymorphisms (SNPs). The method has been utilized to investigate numerous disease conditions from chronic kidney disease to cardiovascular disease to cancer. According to Parikh, it provides an excellent approach to discover genetic factors in a population because of the high number of recombinant events the population represents.

Using GWAS methods, the investigators analyzed data from patients at risk for AKI in the hospital setting—760 adults with AKI and 669 adult controls who underwent surgery or received care in the intensive care unit (ICU)—to determine if any SNPs were associated with the development of AKI. The study population was selected from the surgical ICU (TRIBE-AKI study) and the medical ICU (VALID ICU cohort). AKI was defined as a rise in creatinine of 0.3 mg/dL or 50 percent from baseline for at least two days.

After genotyping a total of 992,895 SNPs, the researchers identified six clusters of three or more SNPs on six different chromosomes that are associated with a patient's risk of developing AKI. Among these clusters, four (SOX2-OT, IL33, RAB20, and TAOK1) are intronic (not coding information for protein synthesis) and the remaining 2 are intergenic (involving more than one gene). "All six SNP clusters are protective against AKI, with odds ratios ranging from 0.55 to 0.72," said Parikh.

Brigham and Women's Humphreys found the results very intriguing and noted that they could certainly lead to a better understanding of AKI pathophysiology. "Most of the SNP clusters identified appear to protect against AKI," he said. "Understanding how certain gene variants confer renal protection could lead to new therapeutic strategies as well as new risk prediction tools."

"AKI is a heterogeneous disease and genetic studies need to be continued to fully capture the host risk," Dr. Parikh emphasized. "It is recommended that sequencing can be used as a complement to GWAS, to obtain a better map of the genetic variants in GWAS-significant genes or well-established candidate genes."

Although it was a relatively small study by GWAS standards, the results are promising, Humphreys said. "They clearly call for a much larger analysis to rigorously evaluate the association of these candidate SNPs with risk of AKI."

Parikh agreed, adding that "further collaborative research is required utilizing larger cohorts to confirm these findings and identify candidate genes that are mechanistically linked to pathogenesis of AKI."

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Reference

1. Zhao B, et al. Genome-Wide Association Study to Identify Single Nucleotide Polymorphisms Conferring Risk for Acute Kidney Injury. *J Am Soc Nephrol* 25 (Suppl); 2014:7A.