Medical Xpress

Genetic variation increases risk of kidney disease progression in African-Americans

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New research provides direct evidence that genetic variations in some African Americans with chronic kidney disease contribute to a more rapid decline in kidney function compared with white Americans. The research, led by investigators from the University of Maryland School of Medicine and Johns Hopkins University, may help explain, in part, why even after accounting for differences in socioeconomic background, end-stage kidney disease is twice as prevalent among blacks as whites. Results are published online today in the *New England Journal of Medicine*.

"What we found is pretty remarkable—that variations in a single gene account for a large part of the racial disparity in kidney disease progression and risk for end-stage kidney disease," says co-lead author and nephrologist Afshin Parsa, M.D., M.P.H., assistant professor of medicine and member of the Program in Personalized and Genomic Medicine at the University of Maryland School of Medicine. "If it were possible to reduce the effect of this gene, there could be a very meaningful decrease in progressive kidney and end-stage kidney disease within blacks."

Previous landmark discoveries revealed that two common variants within a gene called apolipoprotein L1 (APOL1) were strongly associated with non-diabetic end-stage renal disease in blacks. Having only one copy of the variant APOL1 gene variant is associated with a health benefit – protection against African sleeping sickness, a potentially lethal parasitic infection transmitted by the tsetse fly, found only in sub-Saharan Africa.

However, people with two copies of the variant are at a higher risk for kidney disease.

The current research expands on these prior findings and demonstrates the effect of these variants on the progression of established kidney disease and development of end-stage renal disease; analyzes their role in black-versus-white renal disease disparities; investigates their effect in patients with diabetes and observes the impact of blood pressure control on APOL1-associated disease progression.

According to Dr. Parsa, approximately 13 percent of the African American population has two copies of the risk variants. Fortunately, most of those at risk do not develop kidney disease. The researchers analyzed the role of APOL1 gene variants in two longitudinal studies of patients with kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) and the African American Study of Kidney Disease and Hypertension (AASK), both sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health (NIH). Dr. Parsa examined the CRIC study data, while co-lead author and Johns Hopkins epidemiologist W.H. Linda Kao, Ph.D., M.H.S., analyzed the AASK data.

The ASSK study consisted of nearly 700 non-diabetic African American participants whose kidney disease was attributed to hypertension, a leading cause of kidney failure. The study was initially a clinical trial that tested the effects of different classes of anti-hypertensive medication and two different blood pressure goals on the progression of kidney disease.

"The hypertension intervention had similar effects in persons with and without the high-risk APOL1 variant, suggesting that patients in the APOL1 high risk group still benefit from these drugs," says Dr. Kao. "Blacks with two copies of the high-risk APOL1 variants were at higher

risk for kidney disease progression, but it is important to note that kidney disease in about 40 percent of blacks in the AASK study who also carried the high-risk variants had not progressed at the time of the study. This finding raises the importance of identifying factors that may modify the effect of the APOL1 risk variants."

CRIC expanded on AASK, increasing the number of patients to include those with diabetes, one of the most common causes of kidney failure in the United States. CRIC followed 3,000 white and black patients with renal disease; 46 percent of the participants had diabetes and 48 percent of the participants were of African descent. CRIC compared whites with blacks, with and without the APOL1 risk variants, in diabetics and non-diabetics.

"In CRIC," says Dr. Parsa, "we found that, indeed, the gene variants account for a very significant portion of the faster progression in blacks versus whites. If a person had two copies of the APOL1 risk variant, their kidney disease worsened faster and their chance of developing end-stage kidney disease nearly doubled." The researchers also found that APOL1 variants equally affected progression rates in patients with diabetes, a finding that had not been fully realized in previous studies. "These results suggest that APOL1 gene variants affect the progression of established renal disease, regardless of the primary cause," adds Dr. Parsa.

Beyond that, however, the analysis showed that black patients without the APOL1 high-risk variants still had a slightly increased chance for end-stage renal disease. For this reason, the researchers conclude there may be some remaining unaccounted factors contributing to increased progression of kidney disease in blacks.

Further research will focus on the specific activity of the APOL1 variants. "These gene variants can modify the gene's function. However,

we have not yet been able to delineate how they affect renal disease progression. Our next line of research is to find out what pathways are triggered by these gene variants and how they could cause worsening of renal disease," says Dr. Parsa.

"This study underscores the importance of research examining genetic and racial disparities as part of the effort to improve outcomes by personalizing medicine," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs at the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and Dean of the University of Maryland School of Medicine. "It may lead to targeted treatments tailored to the individual's genetic makeup and could significantly reduce the toll of kidney disease."

An estimated 20 million or more American adults have chronic kidney disease, and over 400,000 people in the United States and 2 million worldwide depend on dialysis to treat kidney failure.

More information: Parsa A, Kao WHL, et al. "APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease." November 9, 2013, at *NEJM*. DOI: 10.1056/NEJMoa1310345

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