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Investigators identify gene associated with kidney disease in African-American population

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Kidney disease is a growing public health problem, with approximately half a million individuals in the United States requiring dialysis treatments to replace the function of their failed kidneys. The problem is particularly acute among African Americans, whose rates of kidney disease are four times higher than those of European Americans.

Now, a scientific team led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and the Universite Libre de Bruxelles, has discovered a genetic explanation - with evolutionary roots - for the higher incidence of kidney disease among African Americans.

As reported in the July 15 online issue of the journal *Science*, the study found that patients with focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (H-ESKD) harbored variants in the APOL1 gene that changed the APOL1 protein sequence. These variants are commonly found in individuals of recent African ancestry.

Furthermore, in a twist of evolutionary medicine, the disease-causing variants may have protected Africans against a lethal parasite, explaining why these genetic variants are so common in the population today.

"We found that the APOL1 risk genes for renal disease occur in more than 30 percent of African-American chromosomes," explains co-senior

author Martin Pollak, MD, Chief of Nephrology at BIDMC and Associate Professor of Medicine at Harvard Medical School. "In fact, the increased risk of kidney disease in individuals who inherited two copies of these variant forms of APOL1 is reported to be approximately 10-fold."

FSGS is a form of injury to the kidney's filtering system, which causes proteins to be lost into the urine and gradually reduces kidney function. ESKD, or end-stage kidney disease, is defined by kidney failure that has progressed to the point that the patient requires dialysis or kidney transplantation.

In 2008, it was discovered that genetic variation near the MYH9 gene on chromosome 22 was associated with increased risk of kidney disease in African-Americans. But, because genome analyses had shown a strong signal of natural selection in the region containing both the MYH9 and APOL1 genes, the authors reasoned that the location of the disease-causing genetic variants was in a broader region. They also predicted that the frequency of these variants would be markedly different between European-Americans and Africans.

Using data from the 1000 Genomes Project DNA ata bank, the authors identified candidate genetic variants and tested for their presence in DNA sample sets. They found that two APOL1 variants - dubbed G1 and G2 - were associated with an increased risk of both FSGS and hypertension-attributed ESKD in African-Americans.

"G1 and G2 both changed the coding sequence of APOL1," explains Pollak. "Further analyses revealed that these very same genetic variants [G1 and G2] conferred human immunity against the parasite responsible for sleeping sickness."

African sleeping sickness is caused by an African trypanosome parasite,

which is transmitted by the tsetse fly. The disease, which produces severe nervous system disorders that can ultimately lead to brain damage, coma and death, is estimated to affect tens of thousands of people, but is not found outside of Africa.

The APOL1 protein circulates in the blood and helps defend against trypanosomes, a finding initially discovered by co-senior author Etienne Pays, PhD, of the Universite Libre de Bruxelles, in Belgium. In the current study, Pays' laboratory found that the plasma from patients harboring the G1 and G2 variants inactivated the trypanosomes that cause the deadliest forms of African Sleeping Sickness, as did the APOL1 protein with these same variants inserted.

"We were excited that our findings appeared to relate kidney disease in the United States with human evolution and parasite infection in Africa," said Pollak. "While there are many details that remain to be clarified in future studies, we do know that sickle-cell disease is a well-established precedent for this model, in which one copy of the mutation confers protection against a parasitic infection but two copies of the mutation can cause severe disease."

As Pollak explains, when present in a single copy, certain hemoglobin mutations protect against malaria. But two copies cause sickle cell disease or thalassemia, severe red-blood cell diseases.

"It appears that we may have found a similar situation in APOL1," he adds. "Consequently, while these genetic variants protect against sleeping sickness, they also greatly increase a person's susceptibility to kidney disease. We hope that these new findings will not only lead us to a better understanding of the underlying mechanisms leading to kidney failure, but will also help us develop new ways to treat trypanosome infection and kidney disease."

Provided by Beth Israel Deaconess Medical Center