Better ways to predict kidney disease risk for African Americans

October 14 2011

Compared to European Americans, African Americans are four to five times more likely to develop kidney failure. Also, family members of African Americans with kidney failure have an increased risk of developing kidney failure, which suggests that genetics may play a role in this skewed risk between races. Previous studies identified variants in a gene called APOL1 that may play a role. The APOL1 gene creates a protein that is a component of HDL, or good cholesterol.

An upcoming issue of the *Journal of the American Society Nephrology* (*JASN*) presents new research on the link between these variants and kidney disease in African Americans. "The five articles published in this issue launch a new era in investigating the underlying risks for developing two very common and complex kidney diseases in African Americans," said Eric G. Neilson M. D., editor-in-chief of *JASN*. "Susceptibility variants such as those in the APOL1 gene give scientists new tools for diagnosing and understanding certain diseases, and they could eventually provide new targets for drug therapy."

The five studies' findings are summarized below.

Ali Gharavi, MD (Columbia University College of Physicians and Surgeons) and his colleagues examined APOL1 gene variants in 74 healthy African Americans and African Americans with various common kidney disorders: 44 with focal segmental glomerulosclerosis (FSGS, which is characterized by scarring of the kidneys), 21 with HIV-

associated nephropathy (HIVAN, a secondary form of FSGS linked with HIV infection), and 32 with IgA nephropathy (which occurs when antibodies build up in the kidneys). Variants in the APOL1 gene often occurred in individuals with FSGS and HIVAN but not in those with IgA nephropathy. "This study confirms that genetic variation in the APOL1 gene is a major risk factor for two forms of kidney disease and that the risk imparted is significant enough that APOL1 testing may be used to determine people's risk for kidney failure," said Dr. Gharavi.

Jeffrey Kopp, MD (National Institutes of Health) and his team studied 271 African American cases of FSGS and HIVAN, 168 European American cases, and 939 healthy individuals. African Americans with variants in both copies of the APOL1 gene had a greatly increased risk of developing FSGS and HIVAN. Approximately 13% of African Americans (more than 3.5 million individuals) carry two APOL1 gene variants, and these individuals have a 4% risk during their lifetime of developing FSGS; those with untreated HIV have a 50% risk during their lifetime of developing HIVAN. "We also found that APOL1-associated FSGS tended to arise at an earlier age and to progress to kidney failure more rapidly than non-APOL1-associated FSGS," said Dr. Kopp.

Martin Pollak, MD (Beth Israel Deaconess Medical Center) and his group looked to see if APOL1 gene variants confer risks for other types of kidney disease among 2,867 African Americans. Nondiabetic individuals with two APOL1 gene variants had a four-fold increased risk of developing chronic kidney disease over nondiabetics without the gene variants. (No increased risk occurred among diabetics.) "Our research shows that APOL1 variants explain the difference between the high rate of kidney disease in African Americans compared with European Americans," said Dr. Pollak.

Dr. Pollak also collaborated with Ravi Thadani, MD (Massachusetts General Hospital) and others to examine whether African Americans

with APOL1 gene variants need dialysis to treat kidney failure at a younger age than those without the variants. Among 407 African Americans with kidney failure, individuals with two gene variants started dialysis at an average age of 49.0 years, compared with 55.9 years for those with one gene variant and 61.8 years for those with no variants. "We may be able to predict when Blacks with kidney disease will experience kidney failure well before it occurs," said Dr. Thadani. These results suggest that patients with two variants may benefit from early therapies to protect their kidneys.

John Sedor, MD (Case Western Reserve University) and his collaborators examined individuals' kidney tissues and found that the protein created by the APOL1 gene resides in different regions of the kidney in patients with FSGS or HIVAN compared to individuals without kidney disease. "Its appearance in the walls of small arteries in the kidney that occurs only in disease suggests that blood vessels may have an underappreciated role in the development and progression of these diseases," said Dr. Sedor.

People inherit two copies of the APOL1 gene -- one from each parent. If they inherit only one copy with a variant, they are resistant to infections caused by a parasite endemic to Africa. For this reason, the variants are common in individuals with African ancestry. Unfortunately, if both copies of the APOL1 gene contain a variant, an individual has an increased risk of kidney failure.

The studies' results provide new information about kidney disease and point to the dangers that African Americans with APOL1 gene variants may face if steps are not taken to protect their kidneys. Early screening and treatment could potentially safeguard against kidney failure and early death for millions of individuals.

More information: www.jasn.asnjournals.org/