Gene variant increases risk of kidney disease in African-Americans

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African-Americans with two copies of the APOL1 gene have about a 4 percent lifetime risk of developing a form of kidney disease, according to scientists at the National Institutes of Health. The finding brings scientists closer to understanding why African-Americans are four times more likely to develop kidney failure than whites, as they reported in the Oct. 13 online edition of the *Journal of the American Society of Nephrology*.

Researchers including Jeffrey Kopp, M.D., at the NIH's National Institute of Diabetes and Digestive and Kidney Diseases and Cheryl Winkler, Ph.D, of the National Cancer Institute have begun tracing the effects of having two variants of the APOL1 gene, which occurs in about 12 percent of African-Americans. Researchers earlier linked this gene to susceptibility for kidney disease. When a person has kidney disease, the kidneys are unable to fully remove waste products and extra water from the blood. The researchers studied a common kidney disease called focal segmental glomerulosclerosis (FSGS), which often progresses to end-stage kidney disease and the need for dialysis or a kidney transplant. The researchers studied FSGS patients who came to the NIH Clinical Center or other collaborating medical centers, and who provided blood samples for genetic studies.

"These findings explain nearly all of the excess risk of non-diabetic kidney failure in African-Americans. African-Americans with no variant or one variant have about the same risk of end-stage kidney disease as their white counterparts," Winkler said. "People with two APOL1 variants have greatly increased risk of particular kidney diseases - by 17- to 30-fold."

The researchers found that African-Americans with two copies of the APOL1 variants have about a 4 percent lifetime risk of developing FSGS. Those who develop kidney disease tend to do so at younger ages than other FSGS patients, with 70 percent diagnosed with FSGS between age 15 and 39, compared to 42 percent in that age group for people with one or no APOL1 variants.

Possessing two APOL1 variants also raises the risk for African-Americans with HIV of developing HIV-associated nephropathy (HIVAN) - a type of kidney disease that develops in some people with human immunodeficiency virus - to 50 percent among those not getting anti-viral therapy. Anti-viral therapy appears fairly effective at preventing HIVAN.

"The much higher risk of kidney disease in patients with HIV suggests that a second hit with a virus or other unknown factor is necessary for kidney injury in people who have two APOL1 variants," Winkler said. This may be why most people with two APOL1 variants do not develop kidney disease.

FSGS patients with two APOL1 variants respond as well to steroid treatments as their counterparts who don't have the variants, making steroids a viable treatment option, the researchers found. Further, they found that kidney disease progresses more rapidly in patients with two APOL1 variants, and they hypothesize that aggressive therapy may be advisable.

"In the future, knowing that you have these gene variants and are at increased risk of developing kidney disease may tell you when to start screening for the disease and how to choose therapy," Kopp said. "However, more research is needed, including clinical trials that test whether early genetic testing in the African-American population makes a difference, whether screening tests for young adults with the variant copies detects kidney disease at an early stage, and whether early treatment affects long-term outcome."

This research builds on earlier advances in understanding the role of genetics in kidney disease. In 2008, Kopp, Winkler and other researchers found that variants in the MYH9 gene

on chromosome 22 are linked to susceptibility to various forms of kidney disease (http://www.nih.gov/news/health/sep2008/niddk-14.htm).

In 2010, working with researchers at Harvard Medical School, among others, Kopp and Winkler found some kidney disease risk is due to variants APOLI, a gene adjacent to MYH9. These variants appear to have evolved about 5,000 years ago in some regions of sub-Saharan Africa to protect against trypanosomal infection, also called African sleeping sickness, a degenerative and potentially fatal disease affecting tens of thousands of people in those regions. People from other continents do not have the APOL1 variants (http://www.nih.gov/news/health/jul2010/niddk-15.htm).

More information: Journal of the American Society of Nephrology online abstract: jasn.asnjournals.org/content/e ….2011040388.abstract

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