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STUDY PROVIDES INSIGHTS INTO THE ROLE OF GENETIC VARIANTS IN KIDNEY DISEASE

Findings may help guide diagnosis and treatment

Highlights

- Among patients with a kidney disease called focal segmental glomerulosclerosis (FSGS), those who had certain genetic variants tended to have more advanced disease when they were diagnosed.
- Patients with the variants responded to cyclosporine and mycophenolate mofetil immunosuppressant treatments just as well as other patients.
- Despite this response to treatment, patients with the variants tended to progress more rapidly to kidney failure than other patients.

Yearly, about 5,000 individuals in the U.S. are diagnosed with FSGS.

Washington, DC (January 8, 2015) — New research provides insights into the ties between certain genetic variants and kidney disease in African Americans. The genetic association is one of the strongest ever reported for a common disease, and these latest findings may help improve diagnosis and treatment. The study appears in an upcoming issue of the *Journal of the American Society of Nephrology* (JASN).

African Americans have a 4-fold increased risk for chronic kidney disease compared with European Americans. Recent work from several research groups has shown that much of this risk is due to genetic variations in a gene called apolipoprotein L1 (*APOL1*), which creates a protein that is a component of HDL, or good cholesterol. These variants arose tens of thousands of years ago in sub-Saharan Africa, and so are present in individuals who have recent sub-Saharan African ancestry. Approximately 5 million African Americans carry *APOL1* risk variants, placing them at increased risk for kidney disease.

Jeffrey Kopp, MD (National Institutes of Health) and his colleagues investigated the role of *APOL1* variants in a particular form of kidney disease called focal segmental glomerulosclerosis (FSGS). The team studied information on 94 patients with FSGS and found that patients who had *APOL1* variants tended to have more advanced disease when they were diagnosed, which fits with prior observations that this genetic form of FSGS progresses rapidly. Previous research has shown that patients with two *APOL1* variants respond to glucocorticoids with reductions in urinary protein excretion, but they

nonetheless may experience progressive loss of kidney function. The present study showed a similar pattern with cyclosporine and mycophenolate mofetil. “New therapies targeting APOL1 injury pathways are needed, as standard therapies do not work for many people with this gene variant,” said Dr. Kopp.

The investigators also found that 72% of self-identified African Americans in the study had *APOL1* risk variants, similar to earlier findings. “We also found the *APOL1* risk genotype in 2 individuals of Hispanic descent, which is well known, and in 2 individuals who self-identified as White, or European American, which has not been reported before. This last finding suggests that *APOL1* risk variants can be present in individuals who self-identify in various ways,” said Dr. Kopp.

In an accompanying editorial, Christopher Larsen, MD (Nephropath) and Barry Freedman, MD, PhD (Wake Forest School of Medicine) write that “the report by Kopp *et al.* enhances our understanding of a common etiology of the FSGS lesion seen on kidney biopsy in African Americans.” They note, however, that the findings from the trial, although informative, are not encouraging due to the poor outcomes that patients with *APOL1* variants often ultimately experience.

Study co-authors include Cheryl Winkler, PhD, Xiongce Zhao, PhD, Milena Radea, PhD, Jennifer Gassman, PhD, Vivette D’Agati, MD, Cynthia Nast, MD, Changli Wei, MD, Jochen Reiser, MD, PhD, Lisa Guay Woodford, MD, Friedhelm Hildebrandt, MD, Marva Moxie-Mims, MD, Debbie Gipson, MD, Aaron Friedman, MD, and Frederick Kaskel, MD.

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The article, entitled “Clinical Features and Histology of Apolipoprotein L1-Associated Nephropathy in the FSGS Clinical Trial,” will appear online at <http://jasn.asnjournals.org/> on January 8, 2015.

The editorial, entitled “Apolipoprotein L1-Associated Nephropathy and the Future of Renal Diagnostics,” will appear online at <http://jasn.asnjournals.org/> on January 8, 2015.

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