**African Americans, ApoL1, and Kidney Disease**

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Remarkable progress was made in the past year toward understanding the African American predisposition to focal segmental glomerulosclerosis (FSGS) and other nondiabetic kidney diseases. Now taking center stage is the need to understand the biology of ApoL1 and to identify additional genetic or environmental factors that may trigger pathogenicity. Such an understanding is crucial to confirm a causal role of ApoL1 variants and examine potential strategies for early detection and transplantation.

It is well known that African Americans have a higher incidence of chronic kidney disease. In 2008, researchers discovered that a region on chromosome 22 was associated with increased risk for nondiabetic kidney diseases (FSGS, HIVAN, and hypertensive CKD) in individuals of African ancestry (1,2). The search for the causal genetic variant initially focused on MYH9, but these studies failed to identify a plausible mechanism for kidney disease pathogenesis. Last year, two groups expanded the search to other genes and identified variants in APOL1, which have a stronger statistical association with risk than MYH9 (3–8) and encode changes to the protein sequence.

APOL1 encodes an apolipoprotein that circulates in the blood bound to HDL particles, and confers resistance to sleeping sickness, an endemic disease in Africa caused by Trypanosoma infection (9). Individuals of African ancestry have two common genetic variations in APOL1 that encode proteins that extend resistance to additional trypanosome species, suggesting a selective advantage is responsible for their frequent occurrence. A single copy of an APOL1 variant is sufficient for resistance to trypanosomiasis; however, two copies of an APOL1 variant substantially increase kidney disease risk. Similar to sickle cell disease, there is a survival and evolutionary advantage in being a heterozygote, but a disadvantage in being a homozygote.

The biology responsible for the association of APOL1 variants with nondiabetic kidney disease is not known. Kidney diseases associated with APOL1 variants are not simple Mendelian disorders, and many individuals with two risk variants do not develop kidney disease. A second hit appears to be required. A population-based study found these risk variants were absent in European Americans, but 13 percent of African Americans have two risk variants, as well as an increased risk of albuminuria and decreased GFR (10). Although ApoL1 is a circulating protein, ApoL1 localizes to podocytes, proximal tubules, and the vasculature of the kidney (11). It is not clear if ApoL1 is synthesized in these kidney cells or absorbed from the circulation, which has important implications in transplantation. One study reported increased graft loss if the donor kidney carried the ApoL1 risk genotype (12), but recipient genotypes were not determined, and it is premature to exclude donors based on APOL1 genotype.

**References**

4. Tour S, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene.