Genetic Variants and Risk of Chronic Kidney Disease

Genetic factors are increasingly recognized to contribute to the risk of chronic kidney disease (CKD), and important differences in the risk of progression to end-stage renal disease (ESRD) have been observed in various racial groups (1). In particular, compared with white patients, African American patients experience kidney failure 4–5 more frequently. Identifying genetic factors that contribute to this increased risk is of major importance in addressing renal disease progression (2).

Seminal investigations led by Martin Pollak and colleagues showed that a locus on chromosome 22 (22q.13) accounts for most of the increased risk of ESRD in black patients. The risk was associated with two variants in the *APOL1* gene. *APOL1* encodes apolipoprotein L1 (ApoL1), which is part of a circulating protein complex that can lyse *Trypanosoma brucei* and other trypanosomes responsible for African sleeping sickness. Although humans are resistant to *T. brucei* because of ApoL1, a virulent subspecies (*T. brucei rhodesiense*) resistant to ApoL1-mediated lysis has emerged. The two variants of *APOL1*, called G1 and G2, confer protection against potentially lethal infections by *T. brucei rhodesiense*, explaining why they are frequent in populations of recent African descent (2). In fact, about 50% of African Americans have one or both of the *APOL1* G1 and G2 risk alleles.

Recently, Parsa *et al.* extended the *APOL1* paradigm by examining the effect of the G1 and G2 variants of *APOL1* on the progression of CKD. Their two prospective multi-center studies—the African American Study of Kidney Disease and Hypertension (AASK), with 693 patients, and the Chronic Renal Insufficiency Cohort Study, with 2955 patients—enrolled individuals with CKD (3). The high-risk group was defined as having 2 copies of the high-risk *APOL1* variants; the low-risk group had 0 copies or 1 copy. A consistent and robust association was observed between the presence of *APOL1* risk variants and higher rates of ESRD and CKD progression in black patients than in white patients regardless of diabetes status. In the AASK study, for instance, patients with 2 copies of *APOL1* risk variants were twice as likely to progress to the composite endpoint of ESRD or a 50% reduction from the estimated baseline glomerular filtration rate over a median follow-up of 9 years. Notably, CKD progression was not influenced by blood pressure control (compared with *APOL1* status), and no interaction was observed between *APOL1* genotype and treatment with an angiotensin converting-enzyme inhibitor.

Those studies confirm the robust association of renal-risk *APOL1* variants with higher rates of ESRD and progression of nondiabetic CKD in black patients compared with white patients. They also demonstrate that, in the context of recent selection pressure for gene variants against pathogens, a risk variant that is relatively frequent might also have a large effect size (2). Future research will be needed to address the mechanism by which ApoL1 causes renal disease (at the moment, we know only that ApoL1 is expressed in the glomerulus) and the reason for the inconsistent effect of *APOL1* genotypes in patients with diabetic kidney disease.

Olivier Devuyst
Deputy Editor

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