Genetic Discovery Shows Pathway of ESRD

Variants in APOL1 gene may explain fourfold higher rate of nondiabetic ESRD in African Americans

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EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY ON HYPERTENSION IN BLACKS

BOSTON – The recent identification of two gene mutations in a cohort of African Americans with nondiabetic kidney disease helps explain the disproportionately higher rates of kidney disease in this population and represents a disease-mechanism pathway that could lead to new treatments and possibly a cure, Dr. David J. Friedman said at the meeting.

Dr. Friedman of Beth-Israel Deaconess Medical Center, Boston, and his colleagues recently reported the association between two independent variants in the apolipoprotein L1 (APOL1) gene on chromosome 22 and focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease in blacks (Science 2010;329:841-5). Not only do the investigators believe that APOL1 is very important to the understanding of nondiabetic renal disease in blacks, "we think the variants in the gene are among the most powerful that have been discovered to date," Dr. Friedman stressed.

The disparity between the rates of end-stage renal disease (ESRD) in blacks and whites in the United States is "incredible," Dr. Friedman stated, noting that the incidence rate is four to five times higher in blacks, according to the 2010 United States Renal Data System annual report. "People have been debating for decades whether the major cause of this disparity is genes or environment. No doubt both are important, but given how strongly this phenotype travels in families, I think we can say with certainty that genes play an important role."

The APOL1 discovery came on the heels of an earlier association linking FSGS, nondiabetic ESRD, and HIV nephropathy in blacks with the MYH9 gene located on the same chromosome, Dr. Friedman explained. "This was quite striking, because we used to think of the three conditions as entirely different diseases, yet each one had exactly the same locus."

Despite the strong association and several years spent looking for causal mutations using fine mapping sequences, the causal variants remained elusive until Dr. Friedman and his colleagues approached the problem from a different perspective. "We asked, 'How could any disease gene that's this deleterious become so common in a population?' We assumed there was something in this [genetic region] that was beneficial once upon a time to human evolution in Africa," he said. Using mathematical techniques, "we realized that because of the effects of natural selection, the disease gene interval was much larger than anyone thought and probably contained at least five genes." Consequently, the investigators tested new variants in other genes for association with renal disease in African Americans, looking specifically for variants that had not yet been documented, he said.

In a cohort of 205 African Americans with biopsy-proven FSGS and no family history of the disease and 180 African American control subjects, "we saw that variants in the neighboring APOL1 gene were much more strongly associated with renal disease, and unlike the MYH9 variants, which were located in regions of the gene that did not encode for protein, the APOL1 variants were protein-coding sequences." The investigators determined that the top two variants almost always co-occurred on the same chromosome and each changed an amino acid somewhere on the protein. "We called this the g1 risk allele, and when we controlled for it, a new variant popped up, which we called the g2 allele," he said. Controlling for both the g1 and g2 alleles, "the entire association of this region disappeared and there was no signal left for MYH9."

The investigators also tested the genetic variants in hypertension-associated ESRD in a larger cohort of 1,030 African Americans with the disease and 1,025 geographically matched control subjects and found that the same two variants had a tremendous impact on the development of the disease. "When combined together, the *P* value was on the order of 10 to the minus 60, or 35 orders of magnitude greater than the very best MYH9 [result]," Dr. Friedman said. Surprisingly, he noted, we found that these disease variants follow a recessive pattern and together the odds ratio was on the order of 7-10, while the very largest effect sizes of the common variants that affect hypertension or diabetes will confer odds ratios of about 1.4-1.5."

The APOL1 gene and these variants "tend to fall into a different category that we've all been familiar with in the past," Dr. Friedman explained. "Most disease variants are either very rare with powerful effects or common with relatively modest effects. The APOL1 variants have a surprising combination of effect size and frequency such that 50%-60% of African Americans carry g1 and/or g2 risk alleles, and 50% are risk homozygous, meaning they are in the highest risk for kidney disease: That translates into about 3.5 million individuals." Further, while the odds ratios for the more common forms of nondiabetic kidney disease in this population range from 7 to 10, "we're starting to see odds ratios in the range of 30 for diseases like HIV nephropathy."

To determine how much of nondiabetic kidney disease can be explained by the genetic variants, the investigators reviewed data from the prospective population-based Dallas Heart Study and compared the outcomes of European American and Caucasian patients, in whom the renal risk alleles are essentially nonexistent, with those of African Americans with zero or one risk allele and those with both risk alleles. Looking at urine protein levels, an indicator of renal microvascular disease, "we found that black individuals with zero or one copy of the risk allele had rates more similar to whites than to blacks with two alleles," Dr. Friedman reported.

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The results were even more striking for actual hard measures of renal function, he said. "Rates of chronic kidney disease or impaired renal function, indicated by glomerular filtration rates less than 60 mL/min per 1.73 m^2, were essentially the same among blacks with zero or one allele and whites, whereas individuals with a risk genotype had a fourfold increase in impaired renal function." Although the study does not include many individuals with ESRD, the investigators hope to look more closely into such patients in future studies, he said.

In their preliminary review of the data, they couldn't "tell any difference between African Americans with zero or one copy of the allele and Caucasians, but African Americans with two renal risk alleles have at least 10-fold increase in kidney failure," Dr. Friedman stated. "To our surprise, this really only applies to nondiabetic kidney disease. The alleles have essentially no effect that we can detect on diabetic renal disease."

This realization led the investigators to revisit the issue of natural selection. It turns out, according to Dr. Friedman, "APOL1 is the genetic source for the immunity factor that protected people from African sleeping sickness, a parasitic infection caused by *Trypanosoma brucei gambiense*." Similar to selection for the gene variants associated with sickle cell anemia, he explained, "inheriting one copy of the APOL1 gene risk variant provides protection from the parasite, while having two copies seems to increase the risk of kidney disease up to 10-fold." Through natural selection, as more people survived African sleeping sickness, the percentage of the population with kidney disease risk variants increased, he said.

The investigators are currently studying the risk variants intensively to figure out how they work. "We think they may differentially regulate processes such as apoptosis, and cell repair may function as a chloride channel in mammalian systems in the same way it does in lysosomes and may affect biological function," Dr. Friedman hypothesized.

In addition to exploring the underlying mechanisms, the potential clinical value of the genetic discovery is also being considered. "This may help us improve risk stratification," Dr. Friedman said. "It's one thing to say that African Americans have a fourfold increased risk of kidney disease. It's better to find the tag SNP [single nucleotide polymorphism] that will tell if an individual might have an increased risk. If you can actually find the causal variant, then you can potentially predict with much higher success who is and is not at risk for kidney failure," he stated. "The problem is that it works pretty well in Western African populations, such as Nigerians, but not as well in East Africans, such as Ethiopians."

One of the main questions that Dr. Friedman and his colleagues currently are pursuing is whether hypertension causes kidney disease in these at-risk individuals or whether hypertension is the result of primary renal vascular disease. "To us, the fact that the very same genetic variants cause hypertension-associated ESRD and FSGS, a primary renal microvascular disease, suggests that these may be the same disease process that we are either catching at different stages or that have different modifiers, and that hypertension in these patients may just be a symptom and not a cause of kidney failure," Dr. Friedman said.

A cure for nondiabetic kidney disease, which accounts for more than $8.2 billion annually in dialysis coasts, may directly result from the APOL1 finding, Dr. Friedman said. "It's that important."

Dr. Friedman reported no financial conflicts of interested related to his presentation. ■